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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

5,076,464

(54) N-Sulfonyl-2-Oxoindole Derivatives Having Affinity for Vasopressin and/or Ocytocin Receptors

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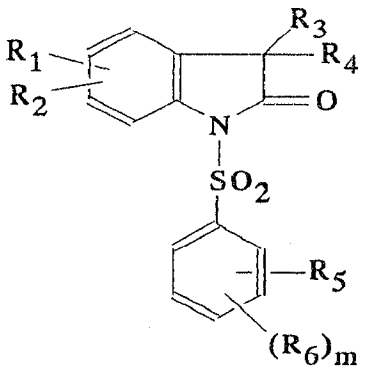
ABSTRACT OF THE DISCLOSURE

The invention relates to N–sulfonyl–2–oxoindole derivatives of formula



(I)

and their possible salts as well as their preparation and the pharmaceutical compositions in which they are present.

These compounds have an affinity for vasopressin and/or ocytocin receptors.

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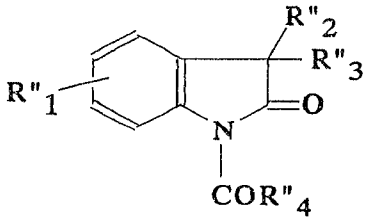
N-sulfonyl-2-oxoindole derivatives, their preparation and the pharmaceutical compositions in which they are present.

The present invention relates to N-sulfonyl-2-oxoindole derivatives, their preparation and the pharmaceutical compositions in which they are present.

International patent application WO 91/01 306 describes 2-oxoindole derivatives which are useful for the treatment of senile dementia. These compounds have the formula

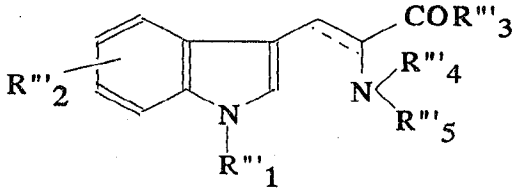


1

in which

- R''_1 is hydrogen, a halogen, an alkyl or an alkoxy;
- R''_2 is hydrogen or a lower alkyl;
- R''_3 is an alkyl, a cycloalkylmethyl, a benzodioxanylmethyl, or an optionally substituted benzyl; and
- R''_4 is a 1-propylbutyl, a pyridyl or an optionally substituted phenyl.

Several patent applications have recently described families of compounds with a non-peptide structure which are active on the vasopressin and/or ocytocin receptors. European applications EP 382 185 and EP 444 945, international application WO 91/05 549 and, more particularly, Japanese patent application JP 03/127732 can be cited in this respect. The latter describes indole-3-propionic acid derivatives of the formula:



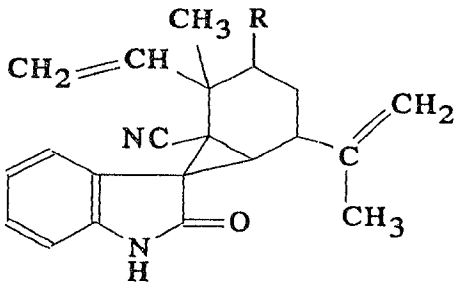
2

in which

- R'''_1 is hydrogen, an alkyl, an alkenyl, a phenylalkyl, a tetrahydrofuryl, an alkoxycarbonyl, an alkoxycarbonylalkyl, a carboxyalkyl or an alkanoyl;
- R'''_2 is hydrogen, a hydroxyl, an alkoxy, an alkyl, a phenylalkyl, a phenylalkoxy or a halogen;
- R'''_3 is a hydrogen, an alkoxy, a free or substituted amino group or an amino acid residue;
- R'''_4 is hydrogen, an alkyl or a phenylalkyl; and
- R'''_5 is a benzoyl, a phenyl, an alkyl, a phenylalkenylcarbonyl, a thienylcarbonyl, a phenylsulfonyl, a pyridylcarbonyl or an imidazolylcarbonyl, it being possible for the phenyl and alkyl groups of the substituent R'''_5 to be substituted.

These compounds are vasopressin antagonists.

Patent US 4,803,217 claims hapalindolinones obtained by fermentation, which are vasopressin antagonists. These compounds have the following formula:



3

in which R is H or Cl.

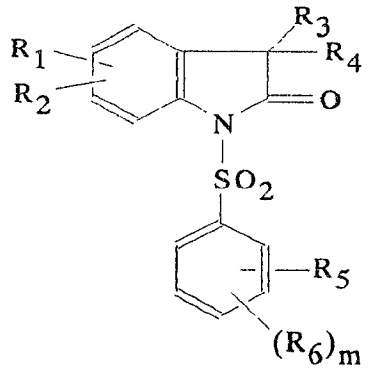
The N-sulfonyl-2-oxoindole derivatives according to the present invention have an affinity for the vasopressin and ocytocin receptors.

Vasopressin is a hormone known for its antidiuretic effect and its effect in regulating the arterial pressure. It stimulates several types of receptors, namely $V_1(V_{1a}, V_{1b})$ and V_2, and thus exerts cardiovascular, hepatic, antidiuretic and platelet-aggregating effects and effects on the central and peripheral nervous systems. Vasopressin receptor antagonists can affect the regulation of the central and peripheral circulations, especially the coronary, renal and gastric circulations, as well as the regulation of hydration and the release of adrenocorticotrophic hormone (ACTH). Non-peptide agonists of vasopressin can advantageously

replace vasopressin or its analogs in the treatment of diabetes insipidus; they can also be used in the treatment of enuresia and in the regulation of hemostasis: treatment of hemophilia and of Von Willebrand's syndrom, antidote to platelet-aggregating agents; Drug Investigation, 1990, 2 (Suppl. 5), 1-47. The vasopressin receptors, like the ocytocin receptors, are also found on the smooth muscle of the uterus. Ocytocin has a peptide structure similar to that of vasopressin. Its receptors are also found on myoepithelial cells of the mammary gland and in the central nervous system (Presse médicale, 1987, 16 (10), 481-485, J. Lab. Clin. Med., 1989, 114 (6), 617-632, and Pharmacol. Rev., 1991, 43 (1), 73-108). This hormone is involved in parturition, lactation and sexual behaviour.

Thus the compounds according to the invention are useful especially in the treatment of complaints of the central and peripheral nervous systems, the cardiovascular system, the renal sphere and the gastric sphere and in disorders of sexual behavior, in humans and animals.

The present invention relates to compounds of the formula



(I)

in which

- R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1-C_4-ω-halogenoalkoxy, a halogen, a C_1-C_4-alkyl, a trifluoromethyl, a C_1-C_7-alkoxy, a C_1-C_4-polyhalogenoalkoxy, a C_2-C_4-ω-hydroxyalkoxy, an ω-methoxyalkoxy in which the alkyl is C_2-C_4, a C_2-C_4-ω-aminoalkoxy which is free or substituted by one or two C_1-C_4-alkyls ; a C_3-C_7-cycloalkyloxy ; a cycloalkylmethoxy in which the cycloalkyl is C_3-C_7 ; a phenoxy; a benzyloxy; a C_1-C_4-alkylthio; a phenylthio; a nitro; an amino which is free or substituted by one or two C_1-C_4-alkyls; a cyano; a C_1-C_4-acyl; a C_1-C_4-acyloxy; a

C_1-C_4-alkylsulfonamido; a phenylsulfonamido; a C_1-C_4-alkylamido; a C_1-C_4-alkoxycarbonylamino; a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1-C_4 alkyls;

- R_3 and R_4 are each independently a C_1-C_6-alkyl, a C_3-C_7-cycloalkyl, a phenyl, a benzyl, a cycloalkylmethyl in which the cycloalkyl is C_3-C_7;

or

- R_3 and R_4 together form a group $-(CH_2)_pX(CH_2)_q-$;

or

- R_3 and R_4, together with the carbon atom to which they are bonded, form an optionally fused, saturated or unsaturated C_3-C_{10} hydrocarbon ring which is unsubstituted or substituted by one or more C_1-C_7-alkyl groups or by a C_3-C_5-spirocycloalkyl;

or else

- R_1 and R_4 each have one of the above meanings and R_2 is located in the 4-position of the indole and forms a group $(CH_2)_3$ with R_3;
- R_5 and R_6 are each independently a hydrogen, a halogen, a C_1-C_7-alkyl, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C_1-C_7-alkyls; a hydroxyamino; a hydroxy; a carboxy; a group OR_7; a group SR_7; a C_1-C_7-acyl; a C_1-C_7-alkoxycarbonyl; a phenoxycarbonyl; a benzyloxycarbonyl; a carbamoyl substituted by groups R'_6 and R''_6; a thiocarbamoyl which is free or substituted by one or two C_1-C_7-alkyls; a sulfamoyl; an alkylsulfamoyl or a dialkylsulfamoyl in which the alkyl is C_1-C_7;-a group $SO_2R'_7$; an alkylsulfonamido in which the alkyl is C_1-C_7; a group COR'_7; a group NR_8R_9; a group $C0-NH-CH(R_{10})-COR_{12}$; if appropriate, the phenyl group forming part of the substitutent R_5 and/or R_6 can be unsubstituted or monosubstituted or polysubstituted by a C_1-C_7-alkyl, a trifluoromethyl, a methoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is C_1-C_4, a carboxy, an alkoxycarbonyl in which the alkyl is C_1-C_7, a C_1-C_7-acyloxy or an imidazolyl;
- R'_6 and R''_6 are each independently hydrogen, a C_1-C_7 alkyl which is unsubstituted or substituted by R'''_6, a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl, a methylpiperidin-4-yl; or R'_6 and R''_6 form, with the nitrogen atom to which they are bonded, a heterocycle selected from piperazine and piperidine;

- R'''_6 is a hydroxy, a cyano, a carboxy which is free or esterified by a C_1–C_7–alkyl or by a benzyl; a phenyl; a pyridyl; a methylpyridyl; an amino which is free or substituted by one or two C_1–C_7–alkyls;
- R_7 is a C_1–C_7–alkyl, a phenyl, a benzyl, a C_3–C_7–cycloalkyl, a C_2–C_4–alkenyl, a C_1–C_7–ω–halogenoalkyl, a C_1–C_7–polyhalogenoalkyl, a C_1–C_7–acyl, a C_1–C_7–ω–carboxyalkyl which is free or esterified by a C_1–C_4–alkyl or by a benzyl, a C_2–C_7 ω–aminoalkyl in which the amino group is free, substituted by one or two C_1–C_4–alkyls or in the form of an ammonium ion;
- R'_7 is a piperazin–1–yl group which is unsubstituted or substituted in the 4–position by a group R''_7, a piperidino group which is unsubstituted or substituted in the 4–position by a group R'''_7, an azetidin–1–yl group which is unsubstituted or substituted in the 3–position by a group R'''_7, a pyridyl group which is unsubstituted or substituted by a methyl;
- R''_7 is a C_1–C_4–alkyl, a phenyl, a benzyl, a C_1–C_4–acyl;
- R'''_7 is R''_7 or an amino which is free or carries a protecting group;
- R_8 and R_9 are each independently a hydrogen, a C_1–C_7–alkyl, a phenyl or a benzyl; R_9 can also be a C_1–C_7–acyl, a C_1–C_7–thioalkyl, a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7, a cycloalkylthiocarbonyl in which the cycloalkyl is C_3–C_7, a C_1–C_4–ω–aminoacyl, a C_1–C_4–ω–hydroxyacyl, a C_1–C_4–ω–benzyloxyacyl, a phenoxycarbonyl, a thienocarbonyl, a pyridylcarbonyl, a methylpyridylcarbonyl, a C_1–C_4–alkoxycarbonyl, a benzoyl, a group $CO–CH(R_{10})–NR_{11}R'_{11}$, a group $CH(R_{10})CO_2R_{11}$, a group $(CH_2)_tCOR_{12}$, a group $CO(CH_2)_tCOR_{12}$, a carbamoyl which is unsubstituted or substituted by a phenyl or one or two C_1–C_4–alkyls;
- m is 1 or, when R_6 is a halogen, a C_1–C_7–alkyl or a C_1–C_7–alkoxy, m can also be 2, 3 or 4 or else $(R_6)_m$ can be m substituents having different meanings selected from halogen, C_1–C_7–alkyl or C_1–C_7–alkoxy;
- p and q are each integers, it being possible for their sum to vary from 3 to 6;
- t is an integer which can vary from 1 to 5;
- X is oxygen, sulfur or a group NR_{13};
- R_{10} is hydrogen, a C_1–C_4–alkyl or a benzyl;
- R_{11} and R'_{11} are each independently hydrogen or a C_1–C_4–alkyl;

- R_{12} is a hydroxy, a C_1–C_4–alkoxy or an amino which is unsubstituted or substituted by one or two C_1–C_4 alkyls;
- R_{13} is hydrogen, a C_1–C_4–alkyl, a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1–C_4 alkyls;

as well as their possible salts.

If a compound according to the invention has one or more asymmetric carbons, the invention includes all the optical isomers of this compound.

The salts of the compounds of formula (I) according to the present invention include those with mineral or organic acids which permit a suitable separation or crystallization of the compounds of formula (I), such as picric acid, oxalic acid or an optically active acid, for example a mandelic acid or a camphosulfonic acid, and mineral or organic acids which form physiologically acceptable salts such as the hydrochloride, hydrobromide, sulfate, hydrogensulfate, di–hydrogenphosphate, maleate, fumarate or naphthalene–2–sulfonate.

The salts of the compounds of formula (I) also include the salts with organic or mineral bases, for example the salts of alkali metal or –alkaline earth metals, such as the sodium, potassium and calcium salts, sodium and potassium salts being preferred, or with an amine such as trometamol, or else the salts of arginine, lysine, or any physiologically acceptable amine.

According to the present invention, halogen is understood as meaning an atom selected from fluorine, chlorine, bromine and iodine, preferably fluorine or chlorine. Amino–protecting group is understood as meaning a group such as, for example, *tert*–butoxycarbonyl, benzyloxycarbonyl or benzyl.

According to the present invention, optionally fused condensed, saturated or unsaturated C_3–C_{10} hydrocarbon ring is understood as meaning various hydrocarbon rings with a monocyclic, dicyclic or tricyclic structure, for example a cyclobutane, a cyclopentane, a cyclohexane, a cycloheptane, a cyclooctane, an indane, a hexahydroindane, an adamantane, a norbornane, a norbornene, a dihydrophenalene, a tricyclo[5.2.1.$0^{2,6}$]decane or a tricyclo[5.2.1.$0^{2,6}$]dec–8–ene.

The compounds of formula (I) in which R_1 is in the 5–position of the indole and R_2 is hydrogen are preferred compounds.

The compounds of formula (I) in which R_1 is a chlorine atom or an ethoxy group in the 5–position of the indole and R_2 is hydrogen are preferred compounds.

The compounds of formula (I) in which R_3 and R_4, together with the carbon to which they are bonded, form a C_3–C_{10} hydrocarbon ring are preferred compounds; particularly preferred compounds are those in which R_3 and R_4, together with the carbon to which they are bonded, form a cycloheptane, an adamantane, a tricyclo[5.2.1.$0^{2,6}$]dec–8–ene or a cyclohexane which is unsubstituted or substituted by a C_3–C_5–spirocycloalkyl or by one or two C_1–C_7–alkyl groups.

The compounds of formula (I) in which R_3 and R_4, together with the carbon to which they are bonded, form a piperidine–4 or N–methylpiperidine–4 ring are also preferred.

The compounds of formula (I) in which R_5 and R_6 are each a methoxy are preferred compounds. Likewise, the compounds in which R_5 in the 2–position is a methoxy and R_6 in the 4–position is a C_1–C_7–acylamino, a C_1–C_4–dialkylureido or an alkoxycarbonylalkylcarbamoyl in which the alkyl groups are C_1–C_7 are preferred compounds.

The following abbreviations are used in the description and in the examples.

DCM : dichloromethane

Ether : ethyl ether

Iso ether : isopropyl ether

Boc : *tert*–butoxycarbonyl

Me, MeO : methyl, methoxy

Et : ethyl

Pr, iPr, nPr : propyl, isopropyl, n–propyl

Bu, iBu, tBu : butyl, isobutyl, *tert*–butyl

Ph : phenyl

Bz : benzyl

Ac : acetyl

AcOEt : ethyl acetate

AcOH : acetic acid

MeOH : methanol

EtOH : ethanol

DMF : dimethylformamide

THF : tetrahydrofuran

DMSO : dimethyl sulfoxide

DIPEA : diisopropylethylamine

TEA : triethylamine

TFA : trifluoroacetic acid

TMEDA : tetramethylethylenediamine

M.p. : melting point

Saline solution : saturated aqueous sodium chloride solution

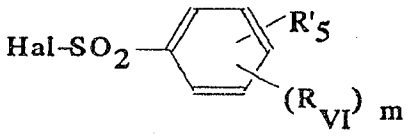
TLC : thin layer chromatography

HPLC : high pressure liquid chromatography

Aqueous hydrochloric acid: dilute hydrochloric acid, about 1 N

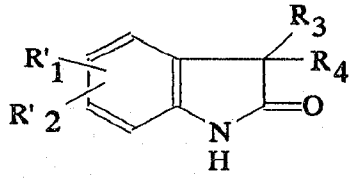
RT : room temperature

The present invention further relates to the method of preparing the compounds according to the invention, characterized in that :
a benzenesulfonyl halide of the formula :



(III)

in which R'_5 and R_{VI} are respectively either R_5 and R_6 as defined above for (I), or precursor groups of R_5 and R_6 is reacted with a 2-oxoindole disubstituted in the 3-position, of the formula :



(II)

in which R'_1 and R'_2 are respectively either R_1 and R_2 as defined above for (I), or precursor groups of R_1 and R_2, and R_3 and R_4 are as defined above for (I),

- either, if $R'_1=R_1$, $R'_2=R_2$, $R'_5=R_5$ and $R_{VI}=R_6$, the resulting compound of formula (I) is isolated;
- or, if any one of the groups R'_1, R'_2, R'_5 and R_{VI} is respectively a precursor group of R_1, R_2, R_5 and/or R_6, the compound obtained is subjected to a subsequent treatment in order to prepare the compound of formula (I) by

conversion of any one of the groups R'_1, R'_2, R'_5 and R_{VI} to R_1, R_2, R_5 and R_6, respectively.

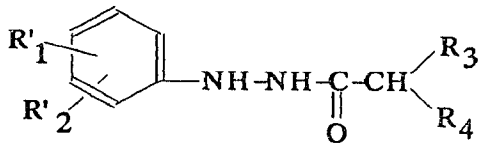
The reaction is carried out in an anhydrous solvent such as DMF or THF, in the presence of a metal hydride such as, for example, sodium hydride, or in the presence of an alcoholate such as potassium *tert*-butylate.

The 2-oxoindoles (II) can be prepared using different procedures. Some of these compounds are novel and form part of the invention.

Compounds (II) in which R'_1 and/or R'_2 are a halogen and R_3 and R_4, together with the carbon to which they are bonded, form a spirocyclobutane, a spirocyclohexane or a spirocycloheptane are known, for example in D. W. Robertson et al. J. Med. Chem., 1987, 30 (5), 824-829. Also, 5-chloro-3-spirocyclopentaneindol-2-one is described in US Patent 3,947,451.

To prepare the compounds (II) in the case where R_3 and R_4 are together or separately a hydrocarbon group, it is possible to use the Brunner reaction described by R.F. Moore and S.G.P. Plant in J. Chem. Soc., 1951, 3475-3478, which leads to the preparation of compounds (II) in which CR_3R_4 is a cyclopentane or a cyclohexane.

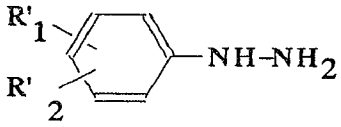
This reaction is carried out by cyclizing a phenylhydrazide derivative of the formula :



(IV)

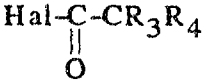
in which R'_1 and R'_2 are as defined above for (II), and R_3 and R_4 have the meanings indicated above for (I), for example by heating in the presence of calcium oxide and quinoline.

According to the same authors, the phenylhydrazide derivative (IV) is obtained by reacting a hydrazine derivative of the formula :



(V)

in which R'_1 and R'_2 have the meanings indicated above for (II), with an acid halide of the formula:



(VI)

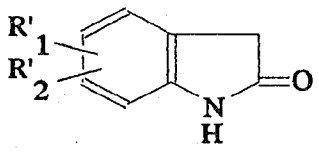
in which R_3 and R_4 have the meanings indicated above for (I).

According to a particular embodiment, if R_3 and R_4, together with the carbon to which they are bonded, form a fused polycyclic hydrocarbon, for example norbornane or norbornene, the reaction is carried out by the method described by J. Wolff et al., Tetrahedron, 1986, 42 (15), 4267–4272: first of all, a lithium salt of the compound (IV) is prepared by reaction with a lithium reagent such as n–butyllithium, in an inert solvent such as THF, at low temperature, and then the cyclization is effected by heating in a solvent such as naphthalene or prehnitene (1,2,3,4–tetramethylbenzene).

The compounds (II) in which $R_1 = R_2 = H$ and CR_3R_4 is adamantane are described in I. Fleming et al., J. Chem. Soc., Perkin Trans I, 1991, 3, 617–626. Thus, the compounds (II) in which R_3 and R_4, together with the carbon atom to which they are bonded, form an adamantane and R_1 and R_2 are other than hydrogen, are novel and form part of the invention. They can be prepared by the method described above.

The hydrazine derivatives (V) are known or are prepared by known methods. The same applies to the acid halides (VI).

A 2–oxoindole disubstituted in the 3–position (II) can also be prepared from a 2–oxoindole of the formula :



(VII)

in which R'_1 and R'_2 are as defined above for (II), by using various methods.

For example, the method described by A.S. Kende and J.C. Hodges in Synth. Commun., 1982, 12 (1), 1–10, involves the addition of an alkylating agent in an appropriate solvent. Thus, to prepare a compound (II) in which $R_3 = R_4$, the reaction is carried out in THF at –75° C, in the presence of TMEDA, by addition of

an alkyllithium such as butyllithium, followed by reaction with a halide of the formula R_3Hal; if R_3 and R_4 are different, the alkylating reaction can be performed in two steps with 2 different alkyl halides of the formulae R_3Hal and R_4Hal. To prepare a compound (II) in which R_3 and R_4 together form a group of the formula $-(CH_2)_n-$, in which n varies from 2 to 7, the reactant used is a compound of formula $Z(CH_2)_nZ$, in which Z is an electron-accepting group such as a halogen, preferably bromine or iodine, a tosyloxy group or a mesyloxy group.

The compounds of formula (II) in which R_3 and R_4 are each independently an alkyl or a phenyl are known. For example, patent DE 3 300 522 describes 5-alkoxy-3,3,-dimethylindol-2-ones.

The compounds of formula (II) in which R_3 and R_4, together with the carbon to which they are bonded, form a C_4-C_8 hydrocarbon ring substituted by one or more C_1-C_7-alkyl groups or by a C_3-C_5-spirocycloalkyl are prepared in the same manner. These compounds are novel and form part of the invention.

If R_3 and R_4 together form a $-(CH_2)_pX(CH_2)_q-$ group, in which p, q and X are as defined above for (I), a 2-oxoindole disubstituted in the 3-position, of formula (II), can be prepared from a 2-oxoindole unsubstituted in the 3-position (VII) by reaction with a compound of the formula :

$$Z-(CH_2)_p-X-(CH_2)_q-Z \qquad \text{(VIII)}$$

in which Z is as defined above and X, p and q are as defined above for (I). The reaction is carried out in the presence of an alcoholate, for example potassium *tert*-butylate, in an anhydrous solvent such as, for example, THF.

If X is a nitrogen atom substituted by a C_1-C_4-acyl, a C_1-C_4-alkoxycarbonyl or a C_1-C_4-alkylcarbamoyl, the substitution on X can be effected either on the 2-oxoindole derivative (II) or on the final compound (I) starting from a compound in which the nitrogen atom (X = NH) is not substituted.

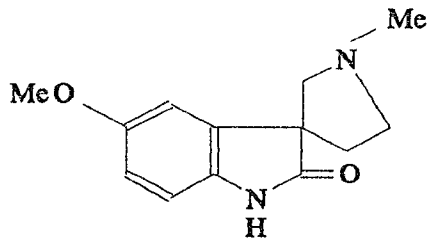
The compounds (I) in which X = NH are preferred compounds according to the invention.

Thus, if X is a nitrogen atom substituted by a C_1-C_4-alkoxycarbonyl, the first step is to prepare a compound (II) or (I) in which X is NH, which is then reacted with the appropriate chloroformate to give the desired compound (II) or (I). In the same way, a C_1-C_4-alkyl isocyanate is reacted with a compound (II) or (I)

in which X = NH to give a 2-oxoindole derivative (II) or a compound (I) in which X is a nitrogen atom substituted by an alkylcarbamoyl. An acid chloride or an anhydride is reacted with a compound (II) or (I) in which X = NH in order to prepare a compound of formula (I) in which X is a nitrogen atom substituted by an acyl.

The compounds (II) in which R_3 and R_4, together with the carbon to which they are bonded, form a pyrrolidine, N-alkylpyrrolidine, piperidine or N-alkylpiperidine ring are described by M. J. Kornet in J. Med. Chem., 1976, 19, (7), 892-899.

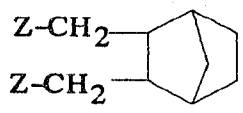
In particular, the horsfiline of the formula :



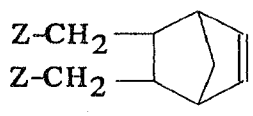
is an alkaloid described in A. Jossang et al., J. Org. Chem., 1991, 56 (23), 6527-6530.

The compounds (II) in which R_3 and R_4, together with the carbon to which they are bonded, form a group $-(CH_2)_pX(CH_2)_q-$ in which p and q are integers whose sum can vary from 3 to 6 and X is oxygen, sulfur or a group NR_{13}, R_{13} being a C_1-C_4-acyl, a benzyl, a C_1-C_4-alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1-C_4 alkyls, are novel and form part of the invention.

To prepare a compound of formula (II) in which R_3 and R_4, together with the carbon to which they are bonded, form a tricyclo[5.2.1.$O^{2,6}$]decane or a tricyclo[5.2.1.$O^{2,6}$]dec-8-ene, a compound of formula (VII') or a compound (VII)" respectively, of the formulae



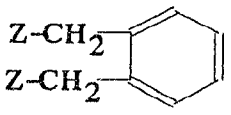
(VII)'



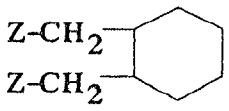
(VII)"

in which Z is as defined above, is reacted with a compound of formula (VII). Compounds (VII)' and (VII)" substituted by one or more C_1–C_4–alkyl groups are used to prepare compounds (II) in which said carbocycles are substituted.

To prepare a compound (II) in which R_3 and R_4, together with the carbon to which they are bonded, form an indane or a hexahydroindane, a compound (VIII)' or a compound (VIII)" respectively, of the formulae



(VIII)'



(VIII)"

in which Z is defined as indicated above for (VIII), is reacted with a compound (VII). Compounds (VIII)' and (VIII)" substituted by one or more C_1–C_4–alkyl groups are used to prepare compounds (II) in which the indane or the hexahydroindane are substituted.

The compounds (II) in which R_3 and R_4, together with the carbon to which they are bonded; form a tricyclo[5.2.1.$0^{2,6}$]decane, a tricyclo[5.2.1.$0^{2,6}$]dec–8–ene, an indane or a hexahydroindane which are unsubstituted or substituted by one or more C_1–C_4–alkyls, are novel and form part of the invention.

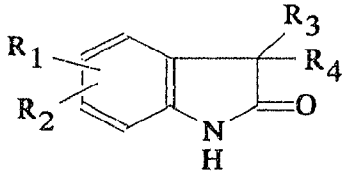
If R_3 and R_4 each are a phenyl, the method described in Helv. Chim. Acta, 1946, 29, 415–432, can be used to prepare a compound (II).

The 2–oxoindole derivatives (VII) are known or are prepared by known methods. An example which may be cited is J. V. RajanBabu in J. Org. Chem., 1986, 51, 1704–1712.

The compounds of formula (II) which carry certain substituents R'_1 and R'_2 on their benzene moiety are used as precursors for the preparation of compounds of formula (II) which carry other substituents R'_1 and R'_2. For example, the compounds (II) in which R'_1 and/or R'_2 = H can be nitrated with the conventional reagents; they can also be acylated by reaction with an acid chloride of formula RCOCl, in which R is a C_1–C_4–alkyl, in the presence of a Lewis acid such as aluminium chloride, in order to prepare a compound (II) in which R'_1 and/or R'_2 = COR. A compound (II) in which R'_1 is an amino group is prepared by catalytic

hydrogenation of a compound (II) in which R'_1 is a nitro group and R'_2 is hydrogen.

The compounds of the formula



(II)'

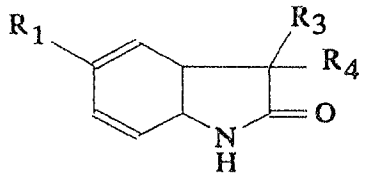
in which

- R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1–C_4–ω–halogenoalkoxy, a halogen, a C_1–C_4–alkyl, a trifluoromethyl, a C_1–C_7–alkoxy, a C_1–C_4–polyhalogenoalkoxy, a C_2–C_4–ω–hydroxyalkoxy, an ω–methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4–ω–aminoalkoxy which is free or substituted by one or two C_1–C_4–alkyls, a C_3–C_7–cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4–alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4–alkyls, a cyano, a C_1–C_4–acyl, a C_1–C_4–acyloxy, a C_1–C_4–alkylsulfonamido, a phenylsulfonamido, a C_1–C_4–alkylamido, a C_1–C_4–alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4–alkyls; and
- R_3 and R_4, together with the carbon to which they are bonded, form
  - . an adamantane,
  - . an indane or a hexahydroindane which are unsubstituted or substituted by one or more C_1–C_7–alkyl groups,
  - . a tricyclo[5.2.1.$0^{2,6}$]decane or a tricyclo[5.2.1.$0^{2,6}$]dec–8–ene which are unsubstituted or substituted by one or more C_1–C_7–alkyl groups, or
  - . a C_4–C_8 hydrocarbon ring substituted by one or more C_1–C_7–alkyl groups or by a C_3–C_5–spirocycloalkyl; or else
- R_3 and R_4 together form a group $-(CH_2)_p-X(CH_2)_q-$ in which p and q are integers whose sum can vary from 3 to 6 and X is oxygen, sulfur or a group NR_{13}, R_{13} being a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1–C_4–alkyls,

with the limitation that if CR_3R_4 is adamantane, R_1 and R_2 are other than hydrogen,

are novel and form part of the invention.

The compounds of the formula



(II)"

in which

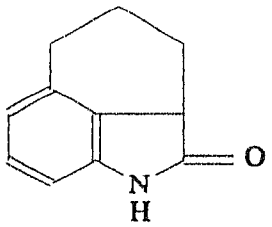
- R_1 is a hydroxy, a C_1–C_4–ω–halogenoalkoxy, a halogen, a C_1–C_4–alkyl, a trifluoromethyl, a C_1–C_7–alkoxy, a C_1–C_4–polyhalogenoalkoxy, a C_2–C_4–ω–hydroxyalkoxy, an ω–methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4–ω–aminoalkoxy which is free or substituted by one or two C_1–C_4–alkyls, a C_3–C_7–cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4–alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4–alkyls, a cyano, a C_1–C_4–acyl, a C_1–C_4–acyloxy, a C_1–C_4–alkylsulfonamido, a phenylsulfonamido, a C_1–C_4–alkylamido, a C_1–C_4–alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4–alkyls;
- R_3 and R_4 together form a group $-(CH_2)_p X(CH_2)_q-$; or
- R_3 and R_4, together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated C_3–C_{10} hydrocarbon ring which is unsubstituted or substituted by one or more C_1–C_4–alkyl groups or by a C_3–C_5–spirocycloalkyl;
- p and q are each an integer, it being possible for their sum to vary from 3 to 6;
- X is oxygen, sulfur or a group NR_{13}; and
- R_{13} is hydrogen, a C_1–C_4–alkyl, a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or 2 C_1–C_4–alkyls,

with the limitation that

- if R_1 is methoxy, CR_3R_4 is other than a pyrrolidine–3 which is unsubstituted or N–substituted by a C_1–C_4–alkyl, and if R_1 is a halogen, CR_3R_4 is other than a pentane,

are novel and form part of the invention.

2a,3,4,5–Tetrahydrobenz[c,d]indol–2(1H)–one of the formula



is commercially available; its derivatives are known or are prepared by known methods.

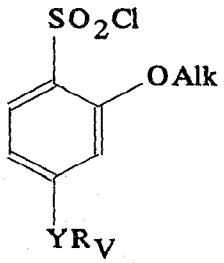
The benzenesulfonyl halides (III) are known and are prepared by known methods. Thus, for example, 4-dimethylaminobenzenesulfonyl chloride is prepared according to C.N. Sukenik et al., J. Amer. Chem. Soc., 1977, 99, 851-858. More generally, the benzenesulfonyl halides (III) in which the substituent R_5 is a dimethylamino group are known or are prepared by known methods; p-benzyloxybenzenesulfonyl chloride is prepared according to European patent application EP 229 566.

The alkoxybenzenesulfonyl chloride is prepared from the sodium alkoxybenzenesulfonate, which is itself prepared by reacting an alkyl halide with sodium hydroxybenzenesulfonate.

2,4-Dimethoxybenzenesulfonyl chloride is prepared according to J. Am. Chem. Soc., 1952, 74, 2008.

The halogenoalkoxybenzenesulfonyl chlorides can be prepared according to patent US 2 540 057.

The benzenesulfonyl halides of the formula



(III)'

in which

- Alk is a C_1-C_7-alkyl;
- Y is O or S; and

- R_V is a C_1–C_7–alkyl, a C_3–C_7–cycloalkyl, a C_2–C_4–alkenyl, a C_1–C_7–ω–halogenoalkyl, a C_1–C_7–polyhalogenoalkyl, a benzyl, a C_1–C_7–acyl or a C_1–C_7–ω–carboxyalkyl esterified by a C_1–C_4–alkyl or by a benzyl,

are novel and form part of the invention.

These compounds are prepared according to D. Hofmann et al. in Liebigs Ann. Chem., 1982, 287–297. Benzene compounds carrying the substituents YR_V and OAlk in the 1– and 3–positions are reacted with trimethylsilyl chlorosulfonate in a solvent such as DCM, at RT. The method of R. Passerini et al. in Gazz. Chim. Ital., 1960, 90, 1277–89, is then applied and this is followed by neutralization, for example with alkali metal carbonate, and then by reaction with a halide such as $POCl_3$ to give the desired benzenesulfonyl halide.

The benzenesulfonyl halides (III) in which the substituent R'_5 is an alkoxycarbonyl, a phenoxycarbonyl, a benzyloxycarbonyl, an alkylthio, a phenylthio, a benzylthio or a group SR_7, R_7 being as defined for (I), are prepared according to Col. Czechoslov. Chem. Commun., 1984, 49, 1184, from an aniline derivative substituted by the same grouping R'_5, said aniline derivative itself being obtained from the corresponding nitrated derivative.

The nitrobenzoic acid derivatives are known; the corresponding alkyl and phenyl esters are obtained by subjecting this acid to an appropriate esterification reaction.

The benzenedisulfonyl dihalides (III, $R'_5 = SO_2Hal$) are known or are prepared by known methods. For example, 2,4–dimethoxybenzene–1,5–disulfonyl dichloride is described in R.J.W. Cremlyn, J. Chem. Soc. C, 1969, 1344.

The halogenoalkoxybenzenesulfonyl chlorides (III, R'_5 = ω–halogenoalkoxy) are used to prepare compounds according to the invention in which the substituent R_5 is an ω–aminoalkoxy which is unsubstituted or substituted by one or two alkyls, according to the following equation:

$$-O-Alk'-Hal + NHR_8R_9 \longrightarrow -OAlk'-NR_8R_9$$

in which Alk' is a C_1–C_4–alkyl.

For certain meanings of the substituents R_1, R_2, R_5 and/or R_6, the compounds (I) according to the invention can be prepared from a precursor of formula (I)' substituted by a group R'_1, R'_2, R'_5 and/or R_{VI}, called a precursor group of R_1, R_2, R_5 and/or R_6.

The description which follows describes the preparation of the compounds of formula (I) carrying substituents R_1 and/or R_5; the same methods apply to the preparation of the compounds in which the substituents R_2 and/or R_6 are defined as indicated for R_1 and R_5.

The compounds (I) in which R_1 and/or R_5 are a hydroxy can be obtained by the catalytic hydrogenation of a compound of formula (I)' in which R'_1 and/or R'_5 are a benzyloxy, for example in the presence of palladium–on–charcoal.

The compounds (I)' in which R'_1 and/or R'_5 are a hydroxy can be used to prepare compounds (I) in which R_1 and/or R_5 are an alkoxy by reaction with an alkyl halide in the presence of a base such as a metal hydride or an alkali metal or alkaline earth metal carbonate like K_2CO_3 or Cs_2CO_3, in a solvent such as THF or DMF. Likewise, the compounds of formula (I) in which R_1 and/or R_5 are an ω–aminoalkyloxy are prepared by reacting an ω–chloroalkylamine with the compounds in which R'_1 and/or R'_5 = OH; similarly, the compounds in which R_1 and/or R_5 are an ω–hydroxyalkoxy are prepared by reaction with a chloroalkyl alcohol; in the particular case of the preparation of a compound (I) in which R_1 and/or $R_5 = O(CH_2)_2OH$, it is also possible to react ethylene carbonate with a compound (I)' in which R'_1 and/or R'_5 = OH.

The compounds of formula (I) in which R_1 and/or R_5 are an acyloxy are obtained by reacting an acid halide or an anhydride with a compound (I)' in which R'_1 and/or R'_5 are a hydroxy.

To prepare compounds of formula (I) in which R_1 and/or R_5 are a monoalkylamino or a dialkylamino, the compounds of formula (I)' in which R'_1 and/or R'_5 are an amino can undergo reductive alkylation. If R'_1 and/or R'_5 are an amino, it is also possible to perform a nitrosation, for example in the presence of nitrous acid or an alkyl nitrite, to prepare a compound (I) in which R_1 and/or R_5 are a diazonium salt; reactions known to those skilled in the art then afford the compounds (I) according to the invention in which R_1 and/or R_5 are a cyano, a halogeno or a C_1–C_4–thioalkyl. Finally, compounds (I) in which R_1 and/or R_5 are one of the groups of the formulae RCONH–, ROCONH–, RNHCONH– and RSO_2NH–, in which R is a C_1–C_4–alkyl, can be prepared by conventional reactions starting from compounds (I)' in which R'_1 and/or $R'_5 = NH_2$

The compounds of formula (I)' in which the substituent R'_5 is a phenoxycarbonyl can be used to obtain the compounds (I) in which R_5 is a phenylcarbamoyl or an alkylcarbamoyl by reaction with an aniline or an alkylamine. A substituted aniline or an alkylamine substituted on the alkyl can be

used to obtain compounds of formula (I) in which R_5 is a phenylcarbamoyl or, respectively, an alkylcarbamoyl substituted on the alkyl.

The compounds of formula (I)' in which R'_5 is a benzyloxycarbonyl can be used to obtain the compounds (I) in which R_5 is a carboxy by catalytic hydrogenation. Reaction with a thionyl halide gives the compounds of formula (I) in which R_5 is a halogenocarbonyl. Such compounds are used to prepare compounds of formula (I) in which R_5 is an N-substituted carbamoyl by reaction with a substituted amine.

The compounds of formula (I) in which R_5 is a group COR''_7 are prepared from corresponding compounds (I)' in which R'_5 is a phenoxycarbonyl by reaction with a substituted piperazine or azetidine.

A compound (I)' in which R'_5 is a nitro group can be used to obtain a compound (I) in which R_5 is an amino group by catalytic hydrogenation, for example in the presence of platinum oxide; other compounds in which the amino group is substituted can then be prepared by using reactions well known to those skilled in the art.

For example, if it is desired to obtain a compound (I) according to the invention in which R_5 is a group NR_8R_9, R_9 being an optionally substituted benzoyl, the benzoyl chloride in which the phenyl carries the appropriate substituent is reacted with a compound (I)' in which R'_5 is an amino group, in the presence of an amine such as triethylamine. For example, 4-chlorosulfonylbenzoyl chloride can be reacted in order to prepare a compound (I)' in which R'_5 is a 4-chlorosulfonylbenzamido group, after which a compound (I) in which the substituent R_5 is a 4-sulfamoylbenzamido group or a 4-alkylsulfamoylbenzamido group is obtained by reaction with ammonia or a C_1-C_4-alkylamine respectively.

In the same way, if it is desired to prepare a compound (I) in which R_5 is a group NR_8R_9, R_9 being a C_1-C_7-acyl, the appropriate anhydride is reacted with a compound (I)' in which R'_5 is an amino group, in the presence of an amine such as triethylamine.

In another preparative example, a compound (I) in which R_5 is an alkylsulfonamido group is obtained by reacting an alkylsulfonyl halide with a compound (I)' in which R'_5 is an amino group.

The compounds of formula (I)' in which R'_5 is an amino group are also useful for the preparation of compounds in which this amino group is substituted by a group $(CH_2)_t$-COR_{12}. In this case, a compound of the formula Hal-$(CH_2)_t$-COOAlk, in which Hal is a halide, for example bromine, and Alk is a C_1-C_4-

alkyl, is reacted with (I)' in the presence of cuprous chloride; if appropriate, the resulting ester is converted to the acid or an amide. The reaction of a lactone, such as butyrolactone or valerolactone, with a compound (I)' in which R'_5 is an amino can be used to prepare the compound (I)' in which $R'_5 = NHCO(CH_2)_tCO_2H$, where t = 2 or 3.

In the same way, the compounds of formula (I) in which R_5 is an amino group substituted by a group $CH(R_{10})CO_2R_{11}$ are prepared by reacting a compound of the formula $Hal-CH(R_{10})CO_2R_{11}$ with the corresponding compounds (I)' in which the substituent R'_5 is an amino.

A compound (I) in which R_5 is an amino group substituted by an alkoxycarbonyl or a phenoxycarbonyl is prepared by reacting an alkyl or phenyl chloroformate with a compound (I)' in which the substituent R'_5 is an amino.

A compound of formula (I) in which R_5 is a ureido is prepared by reacting ammonia with a compound of formula (I)' in which R'_5 is an amino group substituted by a phenoxycarbonyl; a compound of formula (I) in which R_5 is N-phenylureido or N-alkylureido or N,N-dialkylureido in which the alkyl is C_1-C_4 is prepared by reacting an aniline or a C_1-C_4-monoalkylamine or -dialkylamine with such a compound of formula (I)'.

A compound (I) in which R_5 is a carbamoyl which is unsubstituted or substituted by one or 2 alkyl groups is prepared by reacting an appropriate amine with a compound (I)' in which the substituent R'_5 is an amino, in the presence of phosgene.

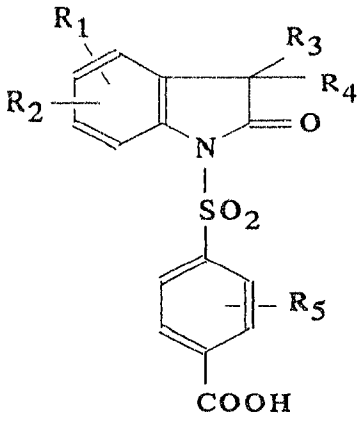
It is also possible to prepare a compound (I) in which R_5 is an amino group substituted by an alkylcarbamoyl or by a phenylcarbamoyl by reacting an alkyl or phenyl isocyanate with a compound (I)' in which the substituent R'_5 is an amino.

Furthermore, a compound (I) in which R_5 is a sulfamoyl group which is unsubstituted or substituted by a C_1-C_4-alkyl is prepared by reacting ammonia or an alkylamine with a compound (I)' in which R'_5 is a halogenosulfonyl group.

The compounds of formula (I)' which are useful as precursors for the preparation of compounds of formula (I) are included in formula (I) and form part of the invention.

Among the compounds of formula (I), the compounds of formulae (IX), (X), (XI), (XII) and (XIII) below, which are useful for the preparation of other compounds of formula (I), are preferred compounds according to the invention.

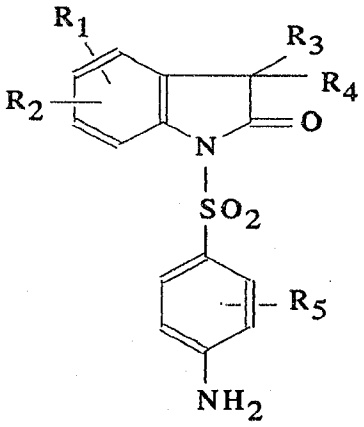
Thus one subject of the present invention consists of the compounds of the formula



(IX)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I), and their functional derivatives such as their esters.

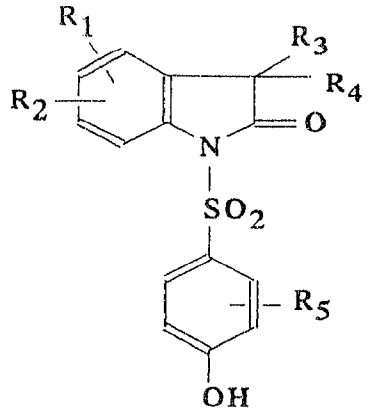
Another subject of the present invention consists of the compounds of the formula



(X)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I), and their salts where appropriate.

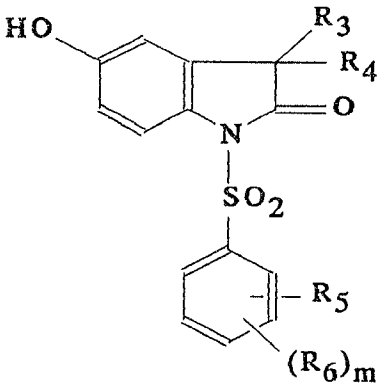
Yet another subject of the present invention consists of compounds of the formula



(XI)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I).

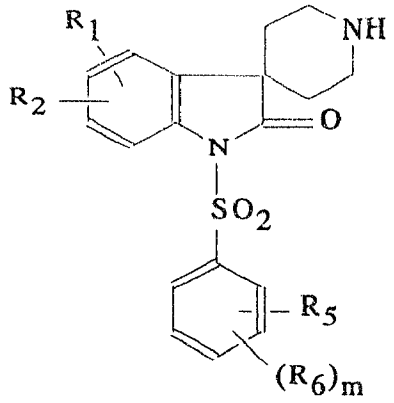
Another subject of the present invention consists of compounds of the formula



(XII)

in which R_3, R_4, R_5, R_6 and m are defined as indicated above for (I).

Yet another subject of the present invention consists of the compounds of the formula



(XIII)

in which R_1, R_2, R_5, R_6 and m are defined as indicated above for (I).

The affinity of the compounds according to the invention for the vasopressin receptors was determined in vitro by using the method described in C.J. Lynch et al., J. Biol. Chem., 1985, 260(5), 2844–2851. This method consists in studying the displacement of tritiated vasopressin bound to the V_1 sites of rat liver membranes. The concentrations of the compounds according to the invention which inhibit the binding of tritiated vasopressin by 50% (IC_{50}) are low, ranging up to 10^{-7} M.

The affinity of the compounds (I) according to the invention for the V_2 receptors was measured on a bovine kidney membrane preparation using a method adapted from P. Crause et al., Molecular and Cellular Endocrinology, 1982, 28, 529–541, and from F.L. Stassen et al., J. Pharmacol. Exp. Ther., 1982, 223, 50–54. The compounds according to the invention inhibit the binding of tritiated arginine–vasopressin to the receptors of the membrane preparation. The IC_{50} values of the compounds according to the invention are low, ranging up to 10^{-9} M.

The activity of the compounds according to the invention as V_2 receptor antagonists was demonstrated by the adenylate cyclase activity assay performed by a method adapted from M. Laburthe et al., Molecular Pharmacol., 1986, 29, 23–27. A bovine kidney membrane preparation is used and each product is incubated for 10 minutes at 37°C, by itself or in the presence of AVP (arginine–vasopressin) at a concentration of 3.10^{-8} M. The cyclic AMP (cyclic adenosine monophosphate) produced is measured by radioimmunoassay. The concentration which causes a 50% inhibition (IC_{50}) of the stimulation of adenylate cyclase induced by 3.10^{-8} M AVP is determined. The IC_{50} values determined are of the order of 10^{-7} M, ranging up to 10^{-8} M.

The activity of the compounds according to the invention, administered orally, as V_2 receptor agonists or antagonists is evaluated in hyperhydrated rats (OFA strain, Sprague–Dawley) treated with vasopressin.

Likewise, the affinity of the compounds (I) according to the invention for the ocytocin receptors was determined in vitro by the displacement of a radioiodinated ocytocin analog bound to the receptors of a gestating rat mammary gland membrane preparation, using a technique similar to that described by J. Eland et al. in Eur. J. Pharmacol., 1987, 147, 197–207. The IC_{50} values of the compounds according to the invention reach 10^{-8} M.

The compounds according to the invention are active after administration by various routes, especially orally.

No sign of toxicity is observed with these compounds at the pharmacologically active doses.

Thus the compounds according to the invention can be used in the treatment or prevention of various vasopressin–dependent or ocytocin–dependent complaints, especially cardiovascular complaints such as hypertension, cardiac insufficiency or coronary vasospasm, in particular in smokers, cardiac ischemia, hemostatic disorders, especially hemophilia, and Von Willebrand's syndrome; complaints of the central nervous system, for example cerebral edemas, depression, anxiety, psychotic states and memory disorders; complaints of the renal system, such as renal vasospasm, necrosis of the renal cortex, hyponatremia and hypokalemia; and complaints of the gastric system, such as hepatocirrhosis, ulcers, the pathology of vomiting, for example nausea, travel sickness or else the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), diabetes insipidus and enuresia. The compounds according to the invention can also be used in the treatment of disorders of sexual behavior; in women, the compounds according to the invention can be used for the treatment of dysmenorrhea or premature labor.

The present invention further relates to pharmaceutical compositions containing an effective dose of a compound according to the invention, or of a pharmaceutically acceptable salt, and suitable excipients.

Said excipients are chosen according to the pharmaceutical form and the desired mode of administration.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, the active principles of formula (I)

above, or their salts where appropriate, can be administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases. The appropriate unit forms of administration include forms for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular or intravenous administration and forms for rectal administration. For topical application, the compounds according to the invention can be used in creams, ointments or lotions.

To obtain the desired prophylactic or therapeutic effect, the dose of active principle can vary between 0.01 and 50 mg per kg of body weight per day.

Each unit dose can contain from 0.5 to 1000 mg, preferably from 1 to 500 mg, of active ingredients in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times a day so as to administer a daily dosage of 0.5 to 5000 mg, preferably 1 to 2500 mg.

If a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances or they can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops can contain the active ingredient in combination with a sweetener, which is preferably calorie-free, and methylparaben and propylparaben as antiseptics, as well as with a flavoring and an appropriate color.

Water-dispersible granules or powders can contain the active ingredient mixed with dispersants or wetting agents or with suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories, which are prepared with binders melting at the rectal temperature, for example cacao butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically

compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

The active principle can also be formulated as microcapsules, if appropriate with one or more carriers or additives.

Apart from the products of formula (I) above or one of the pharmaceutically acceptable salts, the compositions of the present invention can contain other active principles which may be useful in the treatment of the disorders or diseases indicated above.

Thus the present invention further relates to pharmaceutical compositions containing several active principles in association, one of which is a compound according to the invention.

Thus, according to the present invention, it is possible to prepare pharmaceutical compositions containing a compound which is a V1 receptor antagonist in association with a compound which acts on the renin–angiotensin system, such as a converting enzyme inhibitor, an angiotensin II antagonist or a renin inhibitor. They can also be associated for example with a peripheral vasodilator or a calcium inhibitor. Such compositions will be useful in particular in the treatment of hypertension or cardiac deficiency.

Preparation of 2–oxoindoles

Preparation 1:

4,6–Dimethyl–3–spirocyclohexaneindol–2–one

This compound is prepared according to Moore and Plant in J. Chem. Soc., 1951, 3475.

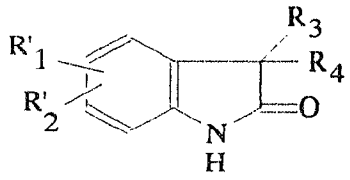
A mixture containing 15 ml of quinoline and 10 g of calcium oxide is refluxed under an inert atmosphere and 5 g of the 3,5–dimethylphenylhydrazide of cyclohexanecarboxylic acid (II, R'_1, $R'_2 = CH_3$, CR_3R_4 = cyclohexane) are added over 30 minutes. The reaction medium is cooled and then poured into an ice/hydrochloric acid mixture. Extraction is carried out with ethyl acetate and the extract is washed with normal hydrochloric acid and with water until the washings are neutral, and then dried and concentrated under vacuum to give a brown solid. Trituration in iso ether gives the expected compound.

M.p. = 223°C.

The indol–2–one derivatives described in Table 1 below are obtained by following the same procedure and varying the starting hydrazide.

These compounds are purified by chromatography on a silica column using DCM as the eluent or by chromatography on an alumina column using DCM or iso ether as the eluent.

TABLE 1



R'1	R'2	CR_3R_4	M.p. °C
5-Cl	H	cyclobutane	191
5-Cl	H	cyclopentane	189
5-Cl	H	cyclohexane	186
H	H	cyclohexane	123-124
$5-CH_3$	H	cyclohexane	164
$5-CH_3O$	H	cyclohexane	226
6-Cl	H	cyclohexane	168
CF_3O	H	cyclohexane	164
$5-C_6H_5O$	H	cyclohexane	160

Preparation 2:

The 3-spirocyclohexaneindol-2-one described in Table 1 above can also be obtained by alkylation of the indol-2-one using the method described below.

A solution of 30 g of indol-2-one in 900 ml of THF is kept at -40°C under a nitrogen atmosphere and 101 g of potassium tert-butylate are added. The temperature is allowed to rise to 0°C over 1 hour, the mixture is then cooled to -60°C and a solution of 52 g of 1,5-dibromopentane in 50 ml of THF is added dropwise. After 30 minutes at -60°C, the temperature is allowed to rise to RT, 30 ml of water are then added and the solvent is evaporated off under reduced pressure. The residue is taken up in 500 ml of DCM and 200 ml of water, the insoluble material is then filtered off and the organic phase is separated off, washed with 100 ml of water, dried over magnesium sulfate and evaporated under vacuum. The residue is

chromatographed on silica using a cyclohexane/ether mixture as the eluent to give the expected compound, which is recrystallized from heptane.

m = 34 g.

M.p. = 123–124°C.

A similar procedure can be applied starting from other indol–2–ones and other alkylating agents.

By way of example, among the starting compounds of formula (VII), 5–chloroindol–2–one is described by Bright in J. Am. Chem. Soc., 1956, 79, 221, and by RajanBabu in J. Org. Chem., 1986, 51, 1704. 4–Chloroindol–2–one can be prepared from 2–chloro–6–nitrotoluene by the method described in J. Am. Chem. Soc., 1956, 78, 221.

5–Methoxyindol–2–one is prepared from 4–methoxyaniline by the method described in J. Am. Chem. Soc., 1974, 96, 5512. In the same way, various indol–2–ones are prepared from the appropriate aniline derivative.

Preparation 3:

5–Ethoxyindol–2–one

A – 3–Thiomethyl–5–ethoxyindol–2–one

23.6 g of ethyl thiomethylacetate in 60 ml of DCM are added to a solution, cooled to about –70°C, of 12.5 g of chlorine in 400 ml of DCM. After stirring for 5 minutes at the same temperature, a solution of 4–ethoxyaniline (48.3 g) in 120 ml of DCM is added. The mixture is stirred for one hour at about 70°C, 39.3 ml of triethylamine are added and the resulting mixture is left to warm up to room temperature. 200 ml of water are added and the organic phase is decanted, dried over magnesium sulfate and evaporated under reduced pressure. The residue is taken up in 500 ml of isopropanol and 20 ml of concentrated hydrochloric acid. The mixture is stirred for about 16 hours at room temperature and filtered and the precipitate is separated off. The filtrate is concentrated under reduced pressure to give the expected product.

B – 5–Ethoxyindol–2–one

The above solid, in 1500 ml of ethanol, is dethiomethylated in the presence of 100 g of Raney nickel (80 to 100 m^2 per g), under reflux, for 3 hours, under a nitrogen atmosphere. The mixture is filtered on talc, the material on the filter is rinsed with 1000 ml of ethanol and the filtrate is concentrated under reduced pressure. 16 g of the expected product are isolated after recrystallization from toluene.

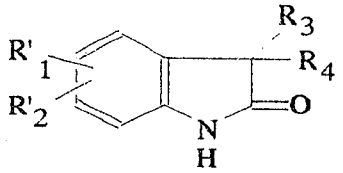
M.p. = 156°C.

The following are isolated in the same manner starting from the corresponding anilines:

5-benzyloxyindol-2-one	m.p. = 152°C
5-n-propylindol-2-one	m.p. = 136°C
5-ethylindol-2-one	m.p. = 152°C
5-(2,2,2-trifluoroethoxy)indol-2-one	m.p. = 145°C

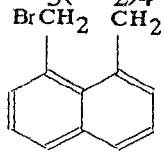
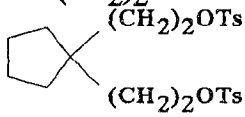
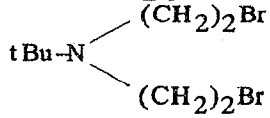
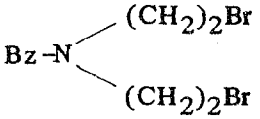
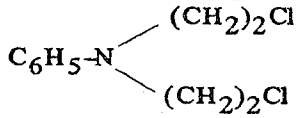
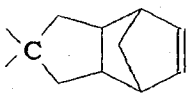
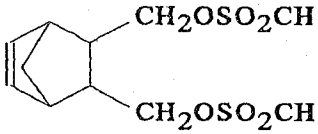
The compounds of formula (II) described below are obtained by following the technique described in Preparation 2 and varying the starting indol-2-one derivative and the alkylating reagent.

TABLE 2



(II)

R'_1	R'_2	CR_3R_4	M.p °C	Alkylating reagent
5-Cl	H	cyclohexane	186-189	$Br(CH_2)_5$ Br
5-Cl	H	cycloheptane	202	$Br(CH_2)_6$ Br
5-Cl	H	4,4-dimethyl cyclohexane	180	$TsO(CH_2)_2C(CH_3)_2$-$(CH_2)_2OTs$
5-Cl	H	2-hexahydroindane	223	cis-1,2-diiodomethylcyclohexane
5-CH_3O	H	4,4-dimethyl cyclohexane	202	$TsO(CH_2)_2C(CH_3)_2$-$(CH_2)_2$-OTs
5-Cl	H	2-indane	228	α,α'-dibromomethyl orthoxylene
5-Cl	H	$C(CH_3)_2$	160	CH_3I
5-Cl	H	$C(CH_2CH_3)_2$	156	CH_3CH_2I
5-Cl	H	C(n Pr)$_2$	158	nPrI
5-Cl	H	C(iBu)$_2$	164	iBuI

5-Cl	H	N-methyl-4-piperidine	260	$Cl(CH_2)_2N(CH_3)-$ $-(CH_2)_2Cl$
5-Cl	H	4-tetrahydro-pyranne	223	$I(CH_2)_2O(CH_2)_2I$
4-Cl	H	cyclohexane	215	$Br(CH_2)_5Br$
5-BzO	H	cyclohexane	162	$Br(CH_2)_5Br$
H	H	$C(CH_2C_6H_5)_2$	206	$C_6H_5CH_2Br$
5-Cl	H	C(n-pentyl)$_2$	142	$CH_3(CH_2)_4Br$
5-Cl	H	2,3-dihydro phenalene-2	–	
5-BzO	H	4,4-dimethyl cyclohexane	154	$TsO(CH_2)_2C(CH_3)_2-$ $-(CH_2)_2OTs$
5-Cl	H	4-spirocyclopentane cyclohexane	202	
5-nPr	H	cyclohexane	151	$Br(CH_2)_5Br$
5-EtO	H	N-tBu-4-piperidine	–	
5-Cl	H	N-Bz-4-piperidine	165	
5-Cl	H	N-phenyl-4-piperidine	188	
5-Cl	H		300	
5-EtO	H	4,4-diethyl cyclohexane	132	$TsO(CH_2)_2C(C_2H_5)_2$ $-(CH_2)_2OTs$
5-EtO	H	cyclohexane	163	$Br(CH_2)_5Br$
5-EtO	H	4,4-dimethyl cyclohexane	178	$TsO(CH_2)_2C(CH_3)_2-$ $-(CH_2)_2OTs$

5-EtO	H	cycloheptane	139	$Br(CH_2)_6Br$
5-Et	H	4,4-dimethyl cyclohexane	160	$TsO(CH_2)_2C(CH_3)_2-(CH_2)_2OTs$
$5-CF_3CH_2O-$	H	4,4-dimethyl cyclohexane	164	ditto
H	H	4,4-dimethyl cyclohexane	169	ditto

Preparation 4:

3-Spiroadamantaneindol-2-one

This compound is prepared according to I. Fleming et al., Tetrahedron Letters, 1982, 2053-2056, from 2-bromoaniline and adamantan-2-one.

Preparation 5:

5-Chloro-3,3-diphenylindol-2-one

This compound is prepared by the method described in Helv. Chim. Acta, 1946, 29, 415-431, by the reaction of benzene with 5-chloroisatin in the presence of aluminum chloride.

M.p. = 281°C.

Preparation 6:

5-Nitro-3-spirocyclohexaneindol-2-one

This compound is prepared by the method described in J. Am. Chem. Soc., 1945, 67, 499, by the nitration of 3-spirocyclohexaneindol-2-one.

M.p. = 192°C.

5-Nitro-3-spiroadamantaneindol-2-one is prepared in the same manner starting from 3-spiroadamantaneindol-2-one.

M.p. > 260°C.

5-Nitro-3-spiro(4,4-dimethyl)cyclohexaneindol-2-one is also prepared.

M.p. = 195°C.

Preparation 7:

5-Amino-3-spirocyclohexaneindol-2-one

This compound is prepared by the method described in J. Chem. Soc., 1951, 3475, by the reduction of 5-nitro-3-spirocyclohexaneindol-2-one, prepared above.

M.p. = 176°C.

5-Amino-3-spiroadamantane is prepared in the same manner.

M.p. = 245°C.

Preparation 8:

5-Fluoro-3-spirocyclohexaneindol-2-one

A - 5-Diazonium-3-spirocyclohexaneindol-2-one tetrafluoroborate

A solution containing 4 g of 5-amino-3-spirocyclohexaneindol-2-one in 9.2 ml of 6 N hydrochloric acid is cooled to 0°C and 2.27 g of sodium nitrite in 2.6 ml of water are added, followed by 2.54 g of sodium tetrafluoroborate in 9 ml of water. After stirring for 5 minutes, the precipitate is filtered off and washed with a 5% solution of tetrafluoroborate, with 3 ml of methanol cooled to about 0°C and then with 5 ml of ether. The salt obtained is dried under vacuum at RT in the presence of phosphorus pentoxide.

B - 5-Fluoro-3-spirocyclohexaneindol-2-one

1 g of the compound obtained in step A is placed in 5 ml of xylene and heated at about 115°C for 2 hours. The mixture is cooled to RT, the precipitate is filtered off and rinsed with toluene and 0.1 g of active charcoal is added to the filtrate. After filtration, the solvent is evaporated off under reduced pressure to give 0.45 g of the expected compound, which is recrystallized from pentane.

M.p. = 114°C.

Preparation 9:

5-Cyano-3-spirocyclohexaneindol-2-one

4.78 g of potassium cyanide and 4.95 g of cuprous cyanide are dissolved at RT in 40 ml of DMSO. The solution is cooled to about 15°C and 4.15 g of the diazonium salt obtained in step A of the previous preparation are added.

After stirring for 30 minutes at RT, 100 ml of water and 100 ml of ether are added and the organic phase is then separated off, dried over magnesium sulfate and evaporated under reduced pressure. The residue is chromatographed on silica using a cyclohexane/ether mixture as the eluent to give the expected compound, which is recrystallized from heptane.

m = 1.4 g.

M.p. = 216°C.

Preparation 10:

5-Chloro-3-spiroadamantaneindol-2-one

1 g of the p-chlorophenylhydrazide of adamantane-2-carboxylic acid is dissolved and 2.5 ml of a solution of n-butyllithium (1.6 M in hexane) are added at -40°C. After stirring for 5 minutes, the mixture is concentrated under vacuum with the temperature being kept below 30°C. 30 ml of 1,2,3,4-tetramethylbenzene are added and the mixture is refluxed for 1 hour. It is concentrated under reduced pressure, the residue is taken up in normal hydrochloric acid, extraction is carried out with ether and the extract is washed, dried and concentrated under vacuum. The oil obtained is chromatographed on a silica column using DCM as the eluent to give 0.3 g of the expected product in the form of a wax, which is crystallized from iso ether.

M.p. = 249°C.

Preparation 11:

5-Chloro-3-cyclohexyl-3-methylindol-2-one

The method described in Synth. Commun., 1982, 12(1), 1-10, is used to prepare 5-chloro-3-cyclohexylindol-2-one as an intermediate, and the expected compound is then obtained by reaction with methyl iodide.

Preparation 12:

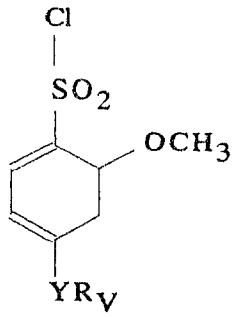
5-Acetyl-3-spirocyclohexaneindol-2-one

2.56 g of acetyl chloride and then 8.25 g of anhydrous aluminum chloride are added to a solution, cooled to 5°C, of 4 g of 3-spirocyclohexaneindol-2-one in 35 ml of 1,2-dichloroethane. The mixture is refluxed for 2 hours, the solvent is evaporated off under reduced pressure and the medium is hydrolyzed with 50 g of ice and extracted with ethyl acetate.

The organic phase is washed with water, dried over magnesium sulfate and then evaporated under reduced pressure. The residue is chromatographed on a silica column using a mixture of heptane and ethyl ether as the eluent to give 3.6 g of the expected product.

M.p. = 192°C.

The benzenesulfonyl chlorides described in the Table below were prepared using the procedure described.



Y	R_V	M.p. °C
S	CH_3	85
O	CH_2Bz	95
O	CH_2CO_2Et	89
O	$(CH_2)_3Br$	106–108

Starting from the various 2–oxoindoles described above and appropriate benzenesulfonyl chlorides, the compounds according to the invention were prepared using the procedures reported in the Examples below.

EXAMPLE 1

5–Chloro–1–(2–methoxy–4–nitrobenzenesulfonyl)–3–spirocyclohexaneindol–2–one

A mixture containing 0.7 g of 5–chloro–3–spirocyclohexaneindol–2–one and 70 mg of sodium hydride in 7 ml of THF is stirred under nitrogen at RT for 30 minutes. 0.7 g of 2–methoxy–4–nitrobenzenesulfonyl chloride is introduced and stirring is maintained at RT for 20 hours. The mixture is concentrated under vacuum, the residue is taken up in 30 ml of water, extraction is carried out with ethyl acetate and the extract is washed with water and then dried and concentrated to give 1.1 g of the expected compound, which crystallizes from iso ether.

M.p. = 188°C.

EXAMPLE 2

1–(4–Amino–2–methoxybenzenesulfonyl)–5–chloro–3–spirocyclohexaneindol–2–one

0.8 g of the compound obtained in the previous Example is reduced with hydrogen under normal pressure at RT for 20 hours in 10 ml of acetic acid, in the presence of 30 mg of platinum oxide. The reaction medium is filtered, the filtrate is concentrated, the residue is taken up in a water/ethyl acetate mixture and the organic phase is washed with water, dried and concentrated. The yellow foam obtained is chromatographed on alumina using DCM as the eluent to give 0.2 g of the expected product.

M.p. = 173°C.

EXAMPLE 3

5-Chloro-1-[4-(2-methylphenylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

A mixture containing 0.2 g of the compound prepared in the previous Example, 0.5 ml of triethylamine, 5 ml of DCM and 0.1 g of orthotoluoyl chloride is stirred at RT for 48 hours. It is concentrated under vacuum, the residue is taken up in a water/ether mixture and left to decant and the organic phase is washed with a saturated solution of sodium hydrogencarbonate and then with water, dried and concentrated under vacuum to give 250 mg of a solid, which is chromatographed on silica using DCM as the eluent to give 0.1 g of the expected product.

M.p. = 192°C.

EXAMPLE 4

6-Chloro-1-(2,4-dimethoxybenzenesulfonyl)-3-spirocyclohexaneindol-2-one

A mixture containing 0.15 g of 6-chloro-3-spirocyclohexaneindol-2-one and 15 mg of sodium hydride in 2 ml of THF is stirred for 30 minutes at RT under nitrogen; 0.15 g of 2,4-dimethoxybenzenesulfonyl chloride is introduced and stirring is maintained at RT for 20 hours. The mixture is concentrated under vacuum, the residue is taken up in 30 ml of water and extracted with ethyl acetate and the extract is washed with water, dried and concentrated under vacuum. The product obtained is recrystallized from iso ether.

M.p. = 147°C.

EXAMPLE 5

Acid fumarate of 5-chloro-1-[4-(3-dimethylaminopropoxy)benzenesulfonyl]-3-spirocyclohexaneindol-2-one

A) 4-(3-Bromopropoxy)benzenesulfonyl chloride

A mixture containing 23 g of sodium 4-hydroxybenzenesulfonate dihydrate, 7 g of potassium hydroxide pellets (85%), 30 ml of water, 50 ml of absolute ethanol, 40 g of 1,3-dibromopropane and 3.4 g of tetrabutylammonium hydrogensulfate is refluxed for 3 hours. The reaction medium is concentrated under vacuum, taken up in ethanol and concentrated once again. The residue is taken up in hot methanol. The insoluble material is filtered off, the filtrate is concentrated and the residue is triturated in ether to give 22.5 g of a white solid. 120 ml of phosphorus oxychloride and 16 g of phosphorus pentachloride are added to this solid and the mixture is stirred for 20 hours at RT and then refluxed for 1 hour. The reaction medium is concentrated under vacuum, the residue is then taken up in an ether/water mixture and the organic phase is decanted and washed with a saturated solution of sodium hydrogencarbonate. After drying and concentration, the expected product is obtained in the form of a yellow oil.

B) 1-[4-(3-Bromopropoxy)benzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

A mixture containing 1.2 g of 5-chloro-3-spirocyclohexaneindol-2-one and 0.16 g of sodium hydride in 6 ml of THF is stirred at RT for 30 minutes under nitrogen. 1.6 g of 4-(3-bromopropoxy)benzenesulfonyl chloride are then added.

After 20 hours at RT, the reaction medium is concentrated under vacuum, the residue is taken up in a water/ethyl ether mixture and decanted and the organic phase is washed with water, dried and concentrated. The oil obtained is purified by chromatography on silica using iso ether as the eluent. The expected product is obtained in the form of an oil, which crystallizes from iso ether.

m = 1 g.

M.p. = 123°C.

C) Acid fumarate of 5-chloro-1-[4-(3-dimethylaminopropoxy)benzenesulfonyl]-3-spirocyclohexaneindol-2-one

A mixture containing 0.5 g of the product obtained in the above step, 0.5 g of potassium iodide and 20 ml of a 33% solution of dimethylamine in methanol is stirred at RT for 20 hours. The reaction medium is concentrated and taken up in 10 ml of water and, after trituration, the insoluble material is separated off and treated with 10 ml of 3 N hydrochloric acid. A gum is formed which is dissolved in 30 ml of warm water, and the solution is filtered on paper and then rendered alkaline by

the addition of 12 N sodium hydroxide. The insoluble material is extracted with ether and the extract is washed, dried and then concentrated to give a yellow oil. This is dissolved in 10 ml of acetone, and 0.1 g of fumaric acid is added to the hot solution.

The expected product precipitates at 20°C.

m = 240 mg.

M.p. = 168°C.

EXAMPLE 6

5-Chloro-1-(2,4-dimethoxybenzenesulfonyl)-3-spiroadamantaneindol-2-one

A mixture containing 0.2 g of 5-chloro-3-spiroadamantaneindol-2-one and 20 mg of sodium hydride in 3 ml of THF is stirred for 30 minutes at RT under a nitrogen atmosphere. 0.18 g of 2,4-dimethoxybenzenesulfonyl chloride is added and stirring is maintained at RT for 20 hours. The reaction medium is concentrated under vacuum, the residue is taken up in 30 ml of water and extracted with ether and the extract is washed with water, dried and concentrated under vacuum. The wax obtained crystallizes from 15 ml of iso ether.

m = 240 mg.

M.p. = 152-154°C.

EXAMPLE 7

5-Chloro-1-(2,4-dimethoxybenzenesulfonyl)-3-spirocycloheptaneindol-2-one

A solution containing 0.156 g of potassium tert-butylate and 0.33 g of 5-chloro-3-spirocycloheptaneindol-2-one in 15 ml of THF is cooled to -40°C under an inert atmosphere. The temperature is allowed to rise to about 10°C over 1 hour, the solution is then cooled to about -40°C, a solution of 0.335 g of 2,4-dimethoxybenzenesulfonyl chloride in 15 ml of THF is added dropwise and the mixture is stirred at RT for 2 hours. The solvent is evaporated off under reduced pressure and the residue is then taken up in 30 ml of DCM and 30 ml of water. The organic phase is separated off, washed with 15 ml of water, dried over magnesium sulfate and evaporated under vacuum. The oil obtained is evaporated under vacuum using a cyclohexane/DCM mixture as the eluent to give the expected compound, which recrystallizes from heptane.

m = 0.51 g.

M.p. = 135°C.

EXAMPLE 8

2,4-Dimethoxy-1-benzenesulfonyl-2a-methyl-2a,3,4,5-tetrahydrobenz[c,d]indol-2-one (I: R_1 = H, $-R_2-R_3 = -(CH_2)_3-$, $R_4 = CH_3$, $R_5 = R_6 = OCH_3$)

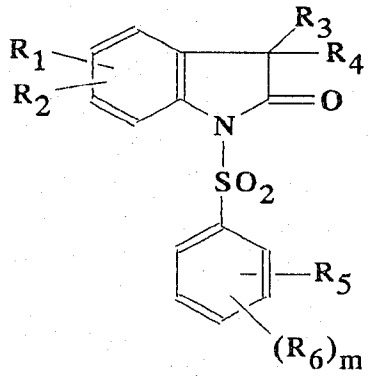
2a,3,4,5-Tetrahydrobenz[c,d]indol-2-one is commercially available. With the temperature maintained at −40°C and under a nitrogen atmosphere, a solution containing 0.7 g of this compound and 1.36 g of potassium tert-butylate in 40 ml of anhydrous THF is prepared.

The temperature is allowed to rise to about 0°C, the solution is then cooled to −60°C and a solution of 0.57 g of methyl iodide in 20 ml of THF is added; the medium is maintained at −10°C for 30 minutes, with stirring, and then cooled to about −40°C and a solution of 0.96 g of 2,4-dimethoxybenzenesulfonyl chloride in 10 ml of THF is added. After stirring for 16 hours at RT, the solvent is evaporated off under reduced pressure and the residue is taken up in 30 ml of DCM and 30 ml of water; the organic phase is separated off and then dried over magnesium sulfate and evaporated. The oil obtained is purified by chromatography on silica using a cyclohexane/DCM mixture as the eluent to give the expected product, which is recrystallized from a cyclohexane/AcOEt mixture (95/5; v/v).

M.p. = 160°C.

The compounds according to the invention collated in Table 3 below were prepared from the 2-oxoindoles described above by following the procedure described in the above Examples.

TABLE 3

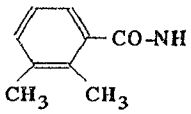
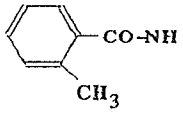
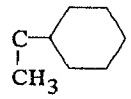
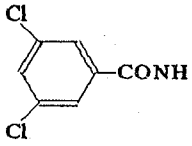
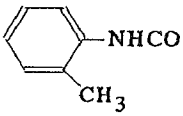


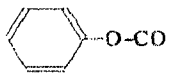
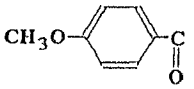
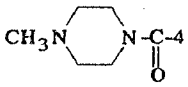
(I)

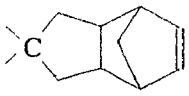
Unless indicated otherwise in the Table below (*), R2 = H and m = 1.

Ex.	R_1	CR_3R_4	R_5	$(R_6)m$	M.p. °C
9	5–Cl	$C(C_6H_5)_2$	3–MeO	4–MeO	178
10	5–NO_2	cyclohexane	3–MeO	4–MeO	157
11	5–Cl	cyclohexane	4–MeO	H	112
12	5–Cl	$C(CH_3)_2$	3–MeO	4–MeO	110
13	5–NH_2	cyclohexane	3–MeO	4–MeO	171
14	5–CN	cyclohexane	2–MeO	4–MeO	148
15	5–Cl	cyclohexane	4–MeO	2,3,6–triMe	188
16	5–Cl	$C(Pr)_2$	2–MeO	4–MeO	186
17	5–Cl	indane–2	2–MeO	4–MeO	182
18	5–Cl	$C(iBu)_2$	2–MeO	4–MeO	184
19	5–Cl	N–methyl piperidine–4	2–MeO	4–MeO	142
20	5–Cl	$C(Et)_2$	2–MeO	4–MeO	190
21	5–F	cyclohexane	2–MeO	4–MeO	149
22	5–Cl	4–tetrahydro–pyranne	2–MeO	4–MeO	142
23	5–Cl	4,4–dimethyl cyclohexane	2–MeO	4–MeO	118

24	5-Cl	2-hexahydro-indane	2-MeO	4-MeO	89
25	4-Cl	cyclohexane	2-MeO	4-MeO	150
26	5-Cl	cyclohexane	3-MeO	4-MeO	152
27	5-Cl	cyclohexane	4-Me	H	150
28	H	cyclohexane	3-MeO	4-MeO	107
29	5-Me	cyclohexane	3-MeO	4-MeO	171
30	5-MeO	cyclohexane	3-MeO	4-MeO	124
31	5-Cl	cyclohexane	2-MeO	4-MeO	149
32	5-Cl	cyclohexane	4-Cl	H	154
33	5-Cl	cyclobutane	3-MeO	4-MeO	111
34	5-Cl	cyclopentane	3-MeO	4-MeO	106
35	5-Cl	cyclohexane	4-MeO	2-Cl	174
36	5-Cl	cyclohexane	4-NO_2	H	172
37	5-Cl	cyclohexane	4-CN	H	198
38	5-Cl	cyclohexane	4-MeO	2-NO_2	147
39	5-Cl	cyclohexane	4-CF_3	H	139
40	5-Cl	cyclohexane	4-CF_3O	H	134
41	5-Cl	cyclohexane	4-MeO	2-NH_2	150

42 *	4-CH_3 R_2=6-CH_3	cyclohexane	4-MeO	2-MeO	165
43	5-Cl	cyclohexane	3-Me	4-BzO	127
44	5-Cl	cyclohexane	4-iPr	2,6-iPr	172
45	5-Cl	cyclohexane	2-CF_3	H	154
46	5-Cl	cyclohexane	2-MeO		215
47	5-Cl	cyclohexane	4-MeO		193
48	5-Cl	cyclohexane	2-MeO	4-CH_3OCO	120
49	5-Cl		2-MeO	4-MeO	184
50	H	adamantane	2-MeO	4-MeO	172
51	5-MeO	4,4-dimethyl cyclohexane	2-MeO	4-MeO	152
52	5-Cl	cyclohexane	2-MeO	4-CH_3SO_2NH	131
53	5-Cl	cyclohexane	2-MeO		240
54	5-Cl	cyclohexane	2-Me	5-F	153
55	5-Cl	cyclohexane	2-CF_3-CH_2O	5-CF_3CH_2O	175
56	5-Cl	cyclohexane	2-MeO		218

57	5–Cl	cyclohexane	2–MeO		165
58	5–Cl	cyclohexane	5–NH_2–SO_2	2,4–di MeO	270
59	5–BzO	cyclohexane	2–MeO	4–MeO	159
60	5–BzO	4,4–dimethyl cyclohexane	2–MeO	4–MeO	142
61	5–Cl	cyclohexane	2–MeO		192
62	5–Cl	cyclohexane	2–MeO		158
64	H	$C(CH_2C_6H_5)_2$	3–MeO	4–MeO	146
65	5–CH_3CO	cyclohexane	3–MeO	4–MeO	122
66	5–Cl	C(n–pentyl)$_2$	2–MeO	4–MeO	140
67	5–Cl	$C(CH_2C_6H_5)_2$	2–MeO	4–MeO	185
68	5–H_2N	cyclohexane	2–MeO	4–MeO	230
69	5–Cl	4–spirocyclo–pentane	2–MeO	4–MeO	154
70	5–Cl	cyclohexane	2–MeO	5–MeO	116
71	5–nPr	cyclohexane	2–MeO	4–MeO	138
72	5–EtO	N–tBu–4–piperidine	2–MeO	4–MeO	95 (0.25 H_2O)
73	5–Cl	N–Bz–4–piperidine	2–MeO	4–MeO	76 (0.5 H_2O)

74	5-Cl	N-phenyl-4-piperidine	2-MeO	4-MeO	163
75	5-Cl	cyclohexane	2-EtO	4-EtO	123
76	5-Cl		2-MeO	4-MeO	190
77	5-EtO	4,4-diethyl cyclohexane	2-MeO	4-MeO	129
78	5-EtO	cycloheptane	2-MeO	4-MeO	130
79	5-EtO	cyclohexane	2-MeO	4-MeO	134
80	5-EtO	4,4-dimethyl cyclohexane	2-MeO	4-MeO	160
81	5-Et	4,4-dimethyl cyclohexane	2-MeO	4-MeO	166
82	5-EtO	4,4-dimethyl cyclohexane	2-MeO	4-NO_2	110
83	5-EtO	4,4-dimethyl cyclohexane	2-MeO	4-NH_2	230
84	5-NO_2	4,4-dimethyl cyclohexane	2-MeO	4-MeO	102
85	5-NH_2	4,4-dimethyl cyclohexane	2-MeO	4-MeO	180
86	5-CF_3CH_2O	4,4-dimethyl cyclohexane	2-MeO	4-MeO	169

EXAMPLE 87

1-(2,4-Dimethoxybenzenesulfonyl)-3-(4,4-dimethylspirocyclohexane)-5-hydroxyindol-2-one

3.51 g of the compound prepared in Example 60 are stirred at 50°C for 1 hour, under a hydrogen atmosphere, with 0.5 g of 10% palladium-on-charcoal in 150 ml of ethanol. The catalyst is filtered off on talc, the material on the filter is rinsed with DCM and the filtrate is evaporated under reduced pressure to give 2.8 g of the expected compound, which is recrystallized from a cyclohexane/AcOEt mixture (90/10; v/v).

M.p. = 220°C.

EXAMPLE 88

1-(2,4-Dimethoxybenzenesulfonyl)-5-hydroxy-3-spirocyclohexaneindol-2-one is prepared in the same manner starting from the 5-benzyloxy derivative described in Example 59.

M.p. = 196°C.

EXAMPLE 80 bis

1-(2,4-Dimethoxybenzenesulfonyl)-3-(4,4-dimethylspirocyclohexane)-5-ethoxyindol-2-one

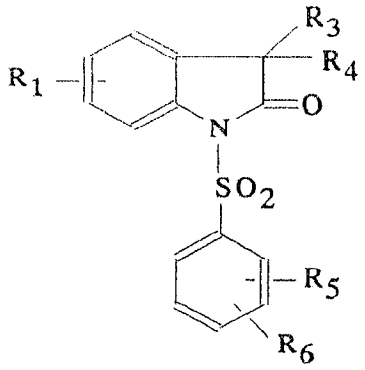
This compound, already described in Example 80, can be prepared by another method starting from the homologous 5-hydroxy compound. 0.6 g of the compound prepared in Example 87 is stirred at RT for 16 hours, under an inert atmosphere, with 0.19 g of anhydrous potassium carbonate and 0.315 g of ethyl iodide in 11 ml of DMF. The solvent is evaporated off under reduced pressure and 30 ml of AcOEt and 30 ml of water are added. The organic phase is washed with water, dried over magnesium sulfate and then concentrated under reduced pressure.

0.45 g of the expected product is obtained by crystallization from cyclohexane.

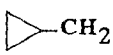
M.p. = 160°C.

The compounds described in Table 4 below are prepared in the same manner.

TABLE 4



(I)

Ex.	R_1	CR_3R_4	R_5	R_6	M.p.°C
89	5-nPrO	cyclohexane	2-MeO	4-MeO	139
90	5-nPrO	4,4-dimethyl cyclohexane	2-MeO	4-MeO	158
91	5-iPrO	4,4-dimethyl cyclohexane	2-MeO	4-MeO	154
92		cyclohexane	2-MeO	4-MeO	155

EXAMPLE 93

5-Acetoxy-1-(2,4-dimethoxybenzenesulfonyl)-3-spirocyclohexaneindol-2-one

0.5 g of the compound prepared in Example 88, 2.5 ml of isopropenyl acetate and 0.165 g of potassium carbonate in 2.5 ml of toluene and 0.3 ml of DMF are heated at about 65°C for 15 hours. After cooling, 10 ml of water and 15 ml of ethyl acetate are added and the organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. 0.51 g of the expected compound, containing 0.5 mol of cyclohexane, is isolated by crystallization from a cyclohexane/ethyl acetate mixture.

M.p. = 116°C.

EXAMPLE 94

1-(2,4-Dimethoxybenzenesulfonyl)-5-(2-hydroxyethoxy)-3-spirocyclohexaneindol-2-one

0.5 g of the compound prepared in Example 88, 0.5 g of ethylene carbonate and 0.272 g of anhydrous potassium carbonate in 1.25 ml of DMF are heated at about 70°C for 40 hours. After cooling, 10 ml of water and 15 ml of ethyl acetate are added and the organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The oily residue is chromatographed on a silica column using a cyclohexane/AcOEt mixture (70/30; v/v) as the eluent to give 0.5 g of the expected product, which is recrystallized from a heptane/DCM mixture.

M.p. = 170°C.

EXAMPLE 95

5-(2-Dimethylaminoethoxy)-1-(2,4-dimethoxybenzenesulfonyl)-3-spirocyclohexaneindol-2-one

0.6 g of the compound prepared in Example 88 is heated at about 40°C for 16 hours, under an inert atmosphere, with 0.32 g of N,N-dimethyl(2-chloroethylamine) and 1.76 g of cesium carbonate in 7.2 ml of acetone and 2.4 ml of DMF. The salts are filtered off and 20 ml of water and 20 ml of AcOEt are added to the filtrate. The organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue is chromatographed on silica using a DCM/MeOH mixture (9/1; v/v) as the eluent to give 0.6 g of the expected product, which is recrystallized from a cyclohexane/iso ether mixture.

M.p. = 122°C.

EXAMPLE 96

5-Chloro-1-(2,4-dimethoxybenzenesulfonyl)-3-(spiropiperidine-4)indol-2-one

This reaction is performed according to J. Org. Chem., 1984, 49, 2795-2799. 0.75 g of 1-chloroethyl chloroformate is added at 0°C to a solution of 1.31 g of the compound described in Example 73 and 0.32 g of 1,8-bis-dimethylaminonaphthalene in 22 ml of 1,2-dichloroethane. The mixture is

refluxed for about 20 minutes and concentrated under reduced pressure to a volume of about 10 ml, and 22 ml of methanol are then added. After refluxing for 50 minutes, the reaction medium is concentrated under reduced pressure and the residue is chromatographed on a silica column using a DCM/MeOH mixture (95/5; v/v) as the eluent. 1.16 g of the expected product are isolated and recrystallized from a mixture of cyclohexane and ethyl acetate.

M.p. = 172°C.

EXAMPLE 97

3-(N-Acetylspiropiperidine-4)-5-chloro-1-(2,4-dimethoxybenzenesulfonyl)indol-2-one

0.086 ml of acetyl chloride is added to a solution, cooled to about 0°C, of 0.35 g of the compound prepared in the previous Example and 0.23 ml of triethylamine in 5 ml of DCM. The mixture is stirred for one hour at 20°C, 5 ml of water are added, the organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced pressure and the residue is chromatographed on a silica column using a DCM/MeOH mixture (99/1; v/v) as the eluent. 0.29 g of the expected product is isolated in the form of the hemihydrate.

M.p. = 107°C.

EXAMPLE 98

5-Chloro-1-(2,4-dimethoxybenzenesulfonyl)-3-(N-methoxycarbonylspiropiperidine-4)indol-2-one

This compound is prepared from the one obtained in Example 96 by reaction with methyl chloroformate.

M.p. = 147°C.

EXAMPLE 99

1-(3,4-Dimethoxybenzenesulfonyl)-5-propionamido-3-spirocyclohexaneindol-2-one

A solution of 0.144 g of propionyl chloride in 3 ml of DCM is added to a solution, cooled to about 0°C, of 0.5 g of the compound described in Example 13 and 0.167 ml of triethylamine in 10 ml of DCM. The mixture is stirred for 2 hours at 20°C, 20 ml of water are then added and the organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced

pressure. 0.5 g of the expected product is isolated after recrystallization from a heptane/AcOEt mixture (95/5; v/v).

M.p. = 158°C.

EXAMPLE 100

1-(3,4-Dimethoxybenzenesulfonyl)-5-(N-methylureido)-3-spirocyclohexaneindol-2-one

0.15 g of methyl isocyanate is added to a solution, cooled to about 0°C, of 0.5 g of the compound described in Example 13 in 10 ml of DCM. After stirring for about 16 hours at RT, 20 ml of water are added and the organic phase is decanted, washed with water, dried over magnesium sulfate and concentrated under reduced pressure. 0.5 g of the expected product is isolated after recrystallization from a mixture of heptane and ethyl acetate.

M.p. = 214°C.

The compound described in the following Example is prepared in the same manner.

EXAMPLE 101

1-(3,4-Dimethoxybenzenesulfonyl)-5-(N-phenylureido)-3-spirocyclohexaneindol-2-one

M.p. = 124°C.

EXAMPLE 102

5-Dimethylamino-1-(2,4-dimethoxybenzenesulfonyl)-3-spirocyclohexaneindol-2-one

A mixture of 0.5 g of the compound described in Example 68 with 0.5 ml of a 35% solution of formaldehyde and 0.12 g of sodium cyanoborohydride in 10 ml of acetonitrile is stirred at RT, under a nitrogen atmosphere, and the pH is adjusted to about 6.5 with a few drops of acetic acid. After 48 hours at 20°C, the solvent is evaporated off under reduced pressure and 20 ml of an approximately 2 N aqueous solution of sodium hydroxide and 20 ml of DCM are added. The organic phase is decanted, washed with water and dried over magnesium sulfate and the solvent is evaporated off under reduced pressure. The residue is chromatographed on a silica column using a cyclohexane/ethyl acetate mixture (80/20; v/v) as the eluent. 0.27 g of the expected product is isolated.

M.p. = 167°C.

EXAMPLE 103

1-(2,4-Dimethoxybenzenesulfonyl)-5-ethylthio-3-spirocyclohexaneindol-2-one

This compound is prepared according to J. Chem. Soc., Chem. Commun., 1980, 16, 756. A mixture of 2.95 g of diethyl disulfide and 0.386 g of isopentyl nitrite is heated to about 80°C, under an inert atmosphere, and 0.8 g of the compound prepared in Example 68 is added. The medium is stirred for one hour at 80°C and then concentrated under reduced pressure. The residue is chromatographed on a silica column using a DCM/cyclohexane mixture (80/20; v/v) as the eluent. The expected product is isolated after crystallization from cyclohexane.

M.p. = 123°C.

EXAMPLE 104

5-Chloro-1-[4-(dimethylaminomethylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

A) 5-Chloro-1-[4-(chloromethylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

0.2 g of the compound prepared in Example 2 is placed in 4 ml of DCM and 0.5 g of TEA at RT and 0.1 g of chloroacetyl chloride is added. After stirring for 20 hours at RT, the mixture is concentrated under vacuum. The concentrate is extracted with ethyl acetate, the extract is washed with water and a solution of sodium carbonate and the residue is then chromatographed on silica using a mixture of DCM and AcOEt as the eluent to give 0.15 g of the expected product.

B) 5-Chloro-1-[4-(dimethylaminomethylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

The compound obtained in the previous step (150 mg) is stirred at RT for 20 hours in 20 ml of a 33% solution of dimethylamine in ethanol. Extraction is carried out with AcOEt and the extract is washed with N sodium hydroxide and then water. The residue is chromatographed on silica using AcOEt as the eluent to give 0.025 g of the expected product.

M.p. = 173°C.

EXAMPLE 105

1-[4-(4-Sulfamoylphenylcarboxamido)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

4-Chlorosulfonylbenzoyl chloride is prepared according to Chem. Ber., 1941, 271.

0.2 g of the compound prepared in Example 2 is brought into contact with 0.5 g of TEA in 5 ml of DCM; 0.13 g of 4-chlorosulfonylbenzoyl chloride is added and the mixture is stirred for 20 hours at RT. It is concentrated under vacuum, the concentrate is taken up in THF, and 10 ml of aqueous ammonia are added. Stirring is continued for a further 20 hours at RT and the mixture is concentrated under vacuum. The residue is extracted with ether and the extract is washed with water, dried over sodium sulfate and then chromatographed on silica using AcOEt as the eluent to give the expected product.

M.p. = 238-242°C after recrystallization from AcOEt.

EXAMPLE 106

1-[4-(3-Sulfamoylphenylcarboxamido)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

A) 3-Chlorosulfonylbenzoyl chloride

This compound is prepared according to patent US 3 290 370. 11 g of chlorosulfonic acid are heated to 60°C and 8 g of phenylchloroform are added dropwise. After heating for 2 hours at 130°C, the mixture is distilled to give 1 g of the expected product.

B.p. = 120-125°C under 0.5 mm Hg.

B) 1-[4-(3-Sulfamoylphenylcarboxamido)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

210 mg of the compound prepared in Example 2 are placed in 10 ml of DCM with 220 mg of the compound obtained in the previous step and 200 mg of TEA, the mixture is stirred overnight and the solvents are then evaporated off under vacuum. The residue is taken up in 20 ml of THF and 20 ml of aqueous ammonia and the mixture is stirred for 6 hours at RT. The solvents are driven off under vacuum and the residue is then taken up in AcOEt and water. Extraction is carried out with AcOEt and the extract is washed with water and then chromatographed on silica using an AcOEt/cyclohexane mixture (50/50; v/v) as the eluent to give the expected product.

M.p. = 176°C.

EXAMPLE 107

1-[4-(2-Carboxyphenylcarboxamido)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

The preparation is carried out according to J. Heterocycl. Chem., 1974, 997-1000.

A mixture containing 0.2 g of the compound prepared in Example 2 with 0.5 ml of TEA and 160 mg of phthalic anhydride is stirred at 60°C for 3 hours. It is concentrated under vacuum and treated with normal hydrochloric acid. The precipitate formed is filtered off and treated with a 10% solution of sodium carbonate; a precipitate forms again, the aqueous phase is decanted and the precipitate is treated with 10% AcOH. The precipitate is filtered off and then washed with 10% AcOH followed by isopropyl ether and recrystallized from iso ether to give the expected product.

m = 0.150 g.

M.p. = 157-158°C.

EXAMPLE 108

1-[4-(Benzyloxymethylcarboxamido)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

This compound is prepared by the procedure described in Example 3 by reacting benzyloxyacetyl chloride with the compound prepared in Example 2.

M.p. = 143°C after recrystallization from iso ether.

EXAMPLE 109

5-Chloro-1-[4-(hydroxymethylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

This compound is obtained by hydrogenating the compound prepared in the previous Example, under the pressure of a water column, in the presence of 5% palladium-on-charcoal in an EtOH/AcOEt mixture.

M.p. = 202°C.

EXAMPLE 110

5-Chloro-1-[4-(imidazol-1-ylphenylcarboxamido)-2-methoxybenzenesulfonyl]-3-spirocyclopentaneindol-2-one

A) Ethyl ester of 4-(imidazol-1-yl)benzoic acid

A mixture containing 35 g of 4-fluorobenzoyl chloride in 50 ml of 100 ethanol is refluxed for 15 minutes. 35 g of the ethyl ester of 4-fluorobenzoic acid obtained are mixed with 22 g of imidazole and 61 g of potassium carbonate in 35 ml of DMSO. The mixture is heated for 18 hours at 120-130°C and 500 ml of iced water are then added. A precipitate forms and the expected product crystallizes from iso ether.

M.p. = 98°C.

B) Imidazol-1-ylbenzoyl chloride

5 g of the ester obtained in step A are refluxed for 2 hours in 20 ml of water and 20 ml of sodium hydroxide solution. The reaction medium is washed with ether and then acidified (pH 2) with concentrated hydrochloric acid. The precipitate formed is filtered off and then washed with iso ether. 5 g of the acid obtained are brought to the reflux temperature in 35 ml of thionyl chloride. The precipitate formed is filtered off and then washed with iso ether to give the expected acid chloride.

M.p. = 243°C.

C) 5-Chloro-1-[4-(imidazol-1-ylphenylcarboxamido)-2-methoxybenzenesulfonyl]-3--spirocyclopentaneindol-2-one

A mixture containing 210 mg of the compound prepared in Example 2 and 200 mg of the acid chloride prepared in step B in 10 ml of DCM and 1.5 ml of TEA is stirred at RT for 1 h and then refluxed for 3 hours. The reaction medium is extracted with DCM and then washed with water and an aqueous solution of sodium hydroxide. After evaporation of the solvents, the residue is chromatographed on silica using a DCM/ methanol mixture as the eluent. The expected product is recrystallized from iso ether.

m = 0.010 g.

M.p. = 145°C.

EXAMPLE 111

5-Chloro-1-[2-methoxy-4-(phenoxycarboxamido)benzenesulfonyl]-3-spirocyclohexaneindol-2-one

This compound is prepared by reacting phenyl chloroformate with the compound prepared in Example 2.

M.p. = 209°C after recrystallization from iso ether.

EXAMPLE 112

5-Chloro-1-[4-(N-methylureido)-2-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

140 mg of the compound obtained in the previous Example are mixed with 5 ml of ethanol, 5 ml of DCM and 5 ml of a 33% solution of methylamine in ethanol. After one hour at RT, the solvents are driven off and the residue is then chromatographed on silica using a DCM/MeOH mixture as the eluent. The product obtained is recrystallized from iso ether.

M.p. = 254°C.

EXAMPLE 113

5-Chloro-1-(2-methoxy-4-ureidobenzenesulfonyl)-3-spirocyclohexaneindol-2-one

A mixture containing 200 mg of the compound prepared in Example 111 with 5 ml of 20% aqueous ammonia, 5 ml of ethanol and 5 ml of DCM is stirred for 1 hour at RT. After filtration of the reaction medium and evaporation of the solvents, the expected product is crystallized from iso ether.

M.p. = 228°C.

EXAMPLE 114

5-Chloro-1-[4-(N-o-tolylureido)-2-methoxy]-3-spirocyclohexaneindol-2-one

A mixture containing 250 mg of the compound prepared in Example 2, 10 ml of xylene and 80 mg of orthotoluyl isocyanate is refluxed for 18 hours. A white precipitate forms and is filtered off. The reaction medium is extracted with ether and the extract is washed with water and then chromatographed on silica using a DCM/MeOH mixture as the eluent. The expected product crystallizes from iso ether.

M.p. = 182°C.

EXAMPLE 115

Benzyl 4-(5-methoxy-2-oxo-3-spirocyclohexaneindol-1-yl)sulfonyl-3-methoxybenzoate

60 mg of sodium hydride are poured in small portions into a mixture containing 500 mg of 3-spirocyclohexane-5-methoxyindol-2-one in 50 ml of THF. After 30 minutes at RT, 800 mg of benzyl 3-methoxy-4-chlorosulfonyl-benzoate chloride are added and the mixture is stirred for 2 hours at RT. The medium is concentrated and taken up in AcOEt and the mixture is washed with water, dried over sodium sulfate and concentrated. The residue is chromatographed on silica using DCM as the eluent.

NMR (at 250 MHz in DMSO):

1.2-1.8 ppm : 10H : cyclohexyl

3.6 ppm and 3.8 ppm : 2 x 3H : 2 x OCH_3

5.4 ppm : 2H : $CO_2-CH_2-C_6H_5$

6.8-8.2 ppm : 11H : aromatic protons

EXAMPLE 116

4-(3-Spirocyclohexane-5-methoxy-2-oxoindol-1-yl)sulfonyl-3-methoxybenzoic acid

600 mg of the compound prepared in the previous Example are placed in 50 ml of AcOEt and hydrogenated at RT and atmospheric pressure in the presence of 140 mg of palladium-on-charcoal to give 310 mg of the expected acid, which is recrystallized from a hexane/ ethanol mixture (70/30; v/v).

M.p. = 210°C.

EXAMPLE 117

5-Chloro-1-[4-(N-(ethoxycarbonylmethyl)carbamoyl)-2-methoxy]-3-spirocyclohexaneindol-2-one

450 mg of ethyl glycinate hydrochloride in 20 mg of sodium methylate are placed in methanol. 200 mg of the compound described in Example 60 in 50 ml of DCM are added and the mixture is stirred at RT for 48 hours. It is extracted with DCM and the extract is washed with water, dried, concentrated and then chromatographed on silica using DCM/MeOH (99.5/0.5; v/v) as the eluent.

M.p. = 164°C.

EXAMPLE 118

1-(4-Carbamoyl-2-methoxybenzenesulfonyl)-5-chloro-3-spirocyclohexaneindol-2-one

300 mg of the compound described in Example 60 are mixed with 5 ml of 30% aqueous ammonia, 10 ml of ethanol and 10 ml of DCM. After 1 hour at RT, the mixture is concentrated and extracted with DCM and the extract is washed with water, dried, concentrated and then chromatographed on silica using DCM/MeOH (99/1; v/v) as the eluent to give 109 mg of the expected product.

M.p. = 160°C.

EXAMPLE 119

5-Chloro-1-[2-methoxy-4-(N-(2-methoxycarbonylethyl)carbamoyl)]-3-spirocyclohexaneindol-2-one

A mixture comprising 320 mg of the compound described in Example 60 and 2 g of methyl aminobispropionate in 30 ml of tetramethylbenzene is refluxed for 30 minutes. It is extracted with AcOEt and the extract is washed with a 1 N solution of hydrochloric acid, dried over sodium sulfate and concentrated. The residue is chromatographed on silica using DCM/MeOH (99/1; v/v) as the eluent to give 100 mg of the expected product.

M.p. = 147°C.

EXAMPLE 120

1-[4-(3-(N-Boc)aminoazetidin-1-ylcarbonyl)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

A mixture containing 300 mg of the compound prepared in Example 60, 900 mg of 3-(N-Boc)aminoazetidine, 1 ml of triethylamine, 10 ml of DCM and 10 ml of methanol is stirred at RT for 1 hour. It is concentrated and extracted with ethyl acetate and the extract is washed with a 1 N solution of hydrochloric acid, dried over sodium sulfate and concentrated. The expected product is obtained after chromatography on silica using DCM/MeOH (99/1; v/v) as the eluent.

M.p. = 136°C.

EXAMPLE 121

1-[4-(3-Aminoazetidin-1-ylcarbonyl)-2-methoxybenzenesulfonyl]-5-chloro-3-spirocyclohexaneindol-2-one

A mixture containing 160 mg of the compound prepared in the previous Example and 3 ml of TFA in 10 ml of DCM is stirred for 30 minutes at RT. The reaction medium is concentrated and crystallized from iso ether and the crystals are filtered off and dried. The product obtained is dissolved in 10 ml of water and then

10 ml of 1 N sodium hydroxide; the solution is extracted with DCM and the extract is washed with water, dried over sodium sulfate and concentrated. The expected product is obtained after chromatography on silica using DCM/MeOH (96/4; v/v) as the eluent.

M.p. = 145°C.

EXAMPLE 122

5-Ethoxy-1-[4-(3-dimethylaminopropoxy)-3-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one hydrochloride

A) 5-Ethoxy-1-[4-(3-bromopropoxy)-3-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one

A mixture containing 0.5 g of 5-ethoxy-3-spirocyclohexaneindol-2-one, 5 ml of THF and 0.07 g of sodium hydride is stirred at 20°C for 15 minutes, 1.65 g of 4-(3-bromopropoxy)-3-methoxybenzenesulfonyl chloride are then added and the resulting mixture is stirred for 20 hours at RT. It is concentrated under vacuum and extracted with ether and the extract is washed with water and then a 10% solution of sodium carbonate. The expected product crystallizes from pentane and is then recrystallized from iso ether.

M.p. = 114-118°C.

B) 5-Ethoxy-1-[4-(3-dimethylaminopropoxy)-3-methoxybenzenesulfonyl]-3-spirocyclohexaneindol-2-one hydrochloride

The compound obtained in the previous step is mixed with 7.5 g of a 33% solution of dimethylamine in ethanol and placed in 10 ml of THF. After stirring for 3 hours, the mixture is concentrated under vacuum and taken up in 10 ml of water and the resulting mixture is extracted with ether. The ether phase is treated with 20 ml of 2 N hydrochloric acid, after which solid potassium carbonate is added to render the solution alkaline to pH 9. The oil which precipitates is extracted with DCM. The expected product crystallizes from ether.

M.p. = 135-138°C.

EXAMPLE 123

1-[4-Aminosulfonamido-2-methoxybenzenesulfony]-5-chloro-3-spirocyclohexaneindol-2-one

0.3 g of the compound prepared in Example 2 is placed in 4 ml of DCM in the presence of 0.5 g of TEA, and 0.3 g of aminosulfonyl chloride, prepared

according to Chem. Ber., 1958, 91, 1339–1341, is added. After stirring for 2 days at RT, the medium is concentrated under vacuum and extracted with ether and the extract is washed with water. After drying, the residue is chromatographed on silica using DCM and then AcOEt as the eluent to give the expected product, which crystallizes from ether.

M.p. = 205–208°C.

EXAMPLES 124 and 125

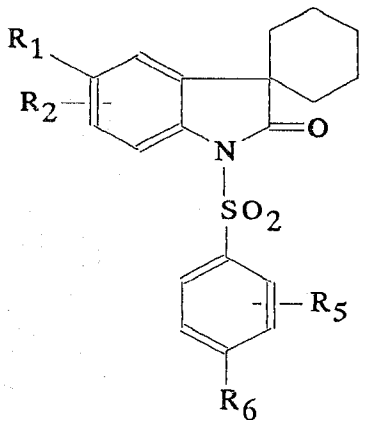
1–(4–Dimethylamino–2–methoxybenzenesulfonyl)–5–methoxy–3–spirocyclohexaneindol–2–one and 1–(4–methylamino–2–methoxybenzenesulfonyl)–5–methoxy–3–spirocyclohexaneindol–2–one

500 mg of 1–(4–amino–2–methoxybenzenesulfonyl)–5–methoxy–3–spirocyclohexaneindol–2–one are mixed with 1 ml of a 37% aqueous solution of formaldehyde, 10 ml of acetonitrile and 430 mg of sodium cyanoborohydride, and 0.12 ml of acetic acid is then added. The temperature of the medium rises and the medium is cooled in an ice bath. Two products of different polarity are formed in succession. 1 ml of an aqueous solution of formaldehyde, 300 mg of sodium cyanoborohydride and 0.12 ml of acetic acid are added to the medium. The mixture is stirred for 1 and a half hours, poured into iced water and then extracted with AcOEt. The extract is washed with water, dried and concentrated to give 2 products, which are separated by chromatography on silica using DCM/AcOEt (98/2; v/v) as the eluent.

M.p. = 210°C (Ex. 124).

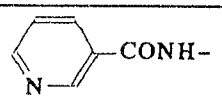
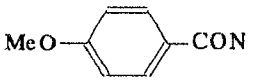
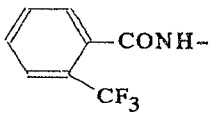
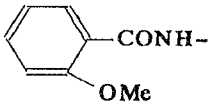
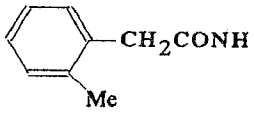
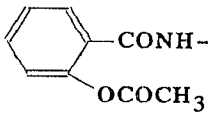
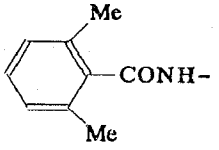
M.p. = 170°C (Ex. 125).

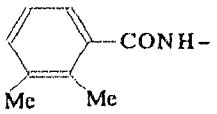
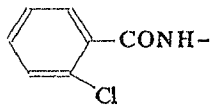
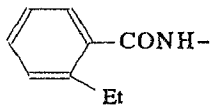
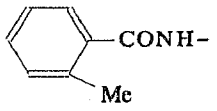
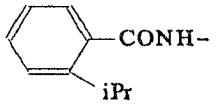
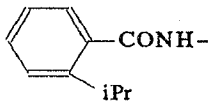
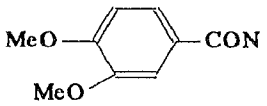
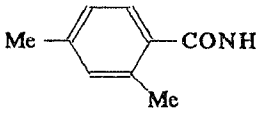
TABLE 5



(I)

Unless indicated otherwise, the substituent R6 is in the 4-position and m = 1.

Ex	R_1	R_2	R_5	R_6	M.p. °C
126	Cl	H	2-MeO		210
127	Cl	H	2-MeO		192
128	Cl	H	2-MeO		188
129	Cl	H	2-MeO		146
130	Cl	H	2-MeO		190
131	Cl	H	2-MeO		147
132	Cl	H	2-MeO	CH_3CONH-	230
133	Cl	H	2-MeO		205
134	Cl	H	2-MeO	$HO_2C(CH_2)_2$-CONH-	205

135	Cl	H	H		180
136	Cl	H	2-MeO		189
137	Cl	H	2-MeO		176
138	MeO	H	2-MeO		245
139	MeO	H	2-MeO		194
140	Cl	H	2-MeO		141
141	Cl	H	2-MeO		140
142	Cl	H	2-MeO		225
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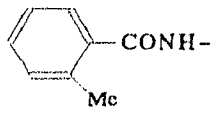
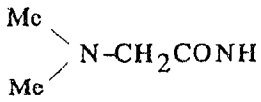
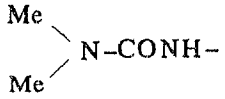
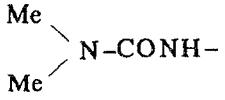
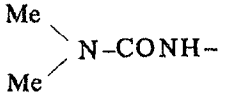
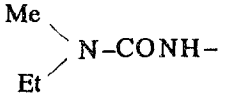
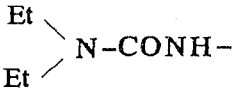
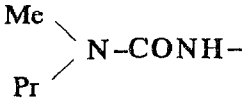
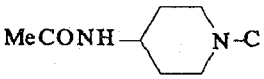
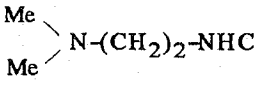
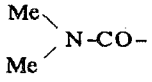
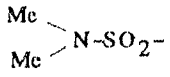
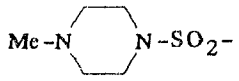
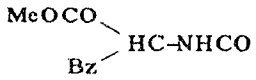
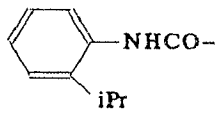
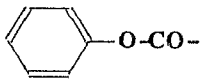
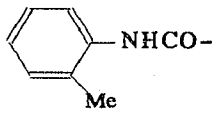
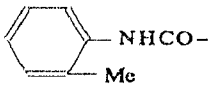
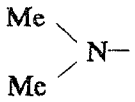
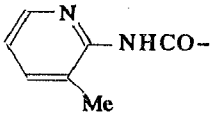
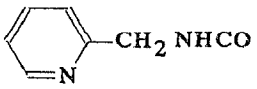
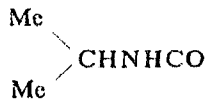
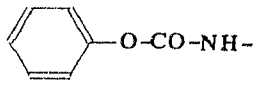
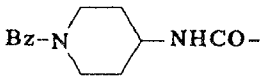
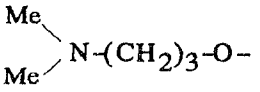
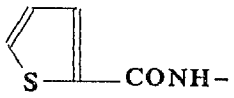
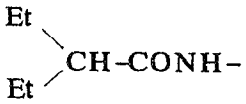
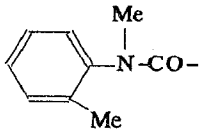
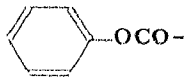
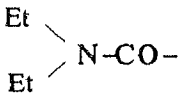
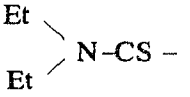
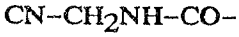
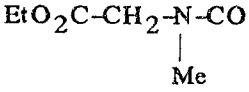
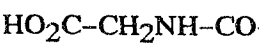
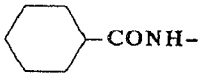
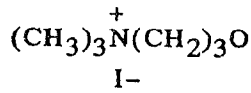
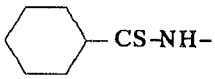
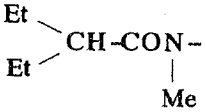
144	MeO	H	2-MeO	$tBuCH_2CONH-$	209

145	EtO	H	2-MeO		223
146	EtO	H	2-MeO		136
147	Cl	H	2-MeO		226
148	CH_3O	H	2-MeO		190
149	EtO	H	2-MeO		192
150	EtO	H	2-MeO		160
151	EtO	H	2-MeO		168
152	EtO	H	2-MeO		137
153	Cl	H	2-MeO		157
154	Cl	H	2-MeO		163
155	Cl	H	2-MeO		192

156	Cl	H	2-MeO		231
157	Cl	H	2-MeO	H	106
158	Cl	H	2-MeO		226
159	Cl	H	2-MeO		117
160	MeO	H	2-MeO	O_2N-	188
161	Cl	H	2-MeO	BzOCO-	NMR
162	Cl	H	2-MeO		215
163	MeO	H	2-MeO	NH_2-	188
164	MeO	H	2-MeO	MeO-	172
165	MeO	H	2-MeO		162
166	MeO	H	2-MeO		198
167	EtO	H	2-MeO	H_2N-	177
168	MeO	6-MeO	2-MeO	MeO-	183

169	EtO	H	2-MeO		150
170	EtO	H	2-MeO	BzOCO-	135
171	EtO	H	2-MeO	HOOC-	NMR
172	EtO	H	2-MeO	MeNHCO-	239
173	EtO	H	2-MeO	5-MeO	131
174	EtO	H	3-MeO	MeO-	127
175	EtO	H	2-MeO		167
176	EtO	H	3-MeO	4,5-di-MeO	130
177	EtO	H	2-MeO		195
178	EtO	H	2-MeO		168
179	EtO	H	2-MeO	N_2O	160
180	EtO	H	2-Me	MeO	176
181	EtO	H	3-MeO	CH_2=CH-CH_2O-	130
182	CF_3O	H	2-MeO	MeO	127

183	EtO	H	2-MeO		171
184	EtO	H	2-MeO	$EtOCOCH_2NHCO$	203
185	EtO	H	2-MeO		181
186	EtO	H	2-MeO	4,5-di-MeO	136
187	EtO	H	2-Me	4-MeO, 5-Cl	129
188	EtO	H	2-MeO		188
189	EtO	H	2-MeO	$HO(CH_2)_2$-NHCO	157
190	EtO	H	2-MeOCO	H	117
191	EtO	H	2-MeO	 , HCl	212
192	EtO	H	2-MeO		181
193	EtO	H	MeO-		206
194	EtO	H	2-MeO	$BzOCOCH_2NHCO$	NMR
195	EtO	H	2-MeO		144

196	EtO	H	2-MeO		152
197	EtO	H	2-MeO		148
198	EtO	H	2-MeO		128
199	EtO	H	2-MeO		232
200	EtO	H	2-MeO		NMR
201	EtO	H	2-MeO		137
202	Cl	H	2-MeO		194
203	EtO	H	2-MeO		214
204	EtO	H	2-MeO		136-140
205	EtO	H	2-MeO		145-150
206	C_6H_5O	H	2-MeO	4-MeO	130
207	EtO	H	2-MeO		210
208	EtO	H	2-MeO		138

209	EtO	H	2-MeO	EtO-CO-CH_2O-	160

The NMR spectra are run in DMSO at 200 MHz.

NMR of Example 161:
1.3-1.8 ppm : 10H : cyclohexyl
3.5 ppm : 3H : OCH_3
5.3 ppm : 2H : O-CH_2-C_6H_5
7.2-8.2 ppm : 11H : aromatic protons

NMR of Example 171:
1.15 ppm : 3H : CH_3
1.19-2 ppm : 10H : cyclohexyl
3.6 ppm : 3H : OCH_3
4 ppm : 2H : OCH_2-CH_3
6.7-8.2 ppm : 6H : aromatic protons

NMR of Example 200:
1-2.2 ppm : 16H : cyclohexyl + $2CH_3$
3 ppm : 3H : NCH_3
4-4.4 ppm : 6H : aromatic protons
6.8-8.2 ppm : 6H : aromatic protons

A resolution of the signals is observed; this is associated with the amide isomerism.

EXAMPLE 210

1-(4-Benzyloxy-2-methoxybenzenesulfonyl)-5-ethoxy-3-spirocyclohexaneindol-2-one

A) Potassium 4-benzyloxy-2-methoxybenzenesulfonate

This preparation is carried out according to K. Hofmann et al., Liebigs Ann. Chem., 1982, 282-297.

10.5 g of 4-benzyloxy-2-methoxybenzene are mixed at 5°C with 30 ml of DCM, and 8 ml of trimethylsilyl chlorosulfonate in 30 ml of DCM are added over 15 minutes at a temperature between 5 and 10°C; after stirring for 15 minutes, 50 g

of ice are added. The mixture is washed with ethyl ether, treated with potassium hydrogencarbonate and then concentrated under vacuum. After drying, the residue is taken up in 150 ml of methanol. The insoluble material is filtered off at the boil and the expected compound then crystallizes at 5°C.

M.p. > 300°C.

The structure of the compound is confirmed by analysis of the NMR spectrum.

B) 4-Benzyloxy-2-methoxybenzenesulfonyl chloride

2.8 g of the compound prepared in the previous Example are mixed with 30 ml of $POCl_3$ and the mixture is refluxed for 3 hours. It is concentrated under vacuum, treated with 20 g of ice and extracted with ethyl ether and the extract is washed with 30 ml of N sodium hydroxide and then water. The medium is concentrated and the oil obtained is then triturated in 30 ml of iso ether. The expected product (0.7 g) crystallizes.

M.p. = 95°C.

C) 1-(4-Benzyloxy-2-methoxybenzenesulfonyl)-5-ethoxy-3-spirocyclohexaneindol-2-one

This compound is prepared by the usual procedure. It crystallizes from iso ether.

M.p. = 135°C.

The structure of the compound is verified by analysis of the NMR spectrum in 2 dimensions (NOESY: Nuclear Overhauser Effect Spectroscopy).

The compound of the next Example is subsequently prepared by debenzylation.

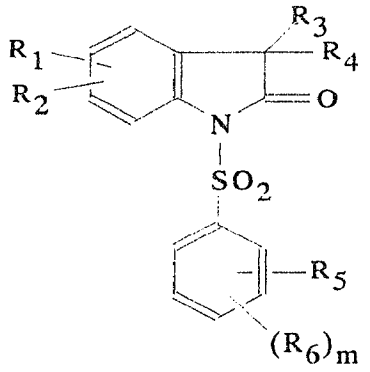
EXAMPLE 211

5-Ethoxy-1-(4-hydroxy-2-methoxybenzenesulfonyl)-3-spirocyclohexaneindol-2-one

M.p. = 209°C.

CLAIMS

1. A compound of the formula



(I)

in which

- R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1–C_4–ω–halogenoalkoxy, a halogen, a C_1–C_4–alkyl, a trifluoromethyl, a C_1–C_7–alkoxy, a C_1–C_4–polyhalogenoalkoxy, a C_2–C_4–ω–hydroxyalkoxy, an ω–methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4–ω–aminoalkoxy which is free or substituted by one or two C_1–C_4–alkyls, a C_3–C_7–cycloalkoxy; a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7; a phenoxy; a benzyloxy; a C_1–C_4–alkylthio; a phenylthio; a nitro; an amino which is free or substituted by one or two C_1–C_4–alkyls; a cyano; a C_1–C_4–acyl; a C_1–C_4–acyloxy; a C_1–C_4–alkylsulfonamido; a phenylsulfonamido; a C_1–C_4–alkylamido; a C_1–C_4–alkoxycarbonylamino; a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4–alkyls;
- R_3 and R_4 are each independently a C_1–C_6–alkyl, a C_3–C_7–cycloalkyl, a phenyl, a benzyl, a cycloalkylmethyl in which the cycloalkyl is C_3–C_7;
  or
- R_3 and R_4 together form a group $-(CH_2)_pX(CH_2)_q-$;
  or
- R_3 and R_4, together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated C_3–C_{10} hydrocarbon ring which is unsubstituted or substituted by one or more C_1–C_7–alkyl groups or by a C_3–C_5–spirocycloalkyl;
  or else

- R_1 and R_4 each have one of the meanings indicated above and R_2 is located in the 4-position of the indole and forms a group $(CH_2)_3$ with R_3;
- R_5 and R_6 are each independently a hydrogen, a halogen, a C_1-C_7-alkyl, a trifluoromethyl, a cyano, a nitro, an amino which is free or substituted by one or two C_1-C_7-alkyls; a hydroxyamino; a hydroxy; a carboxy; a group OR_7; a group SR_7; a C_1-C_7-acyl; a C_1-C_7-alkoxycarbonyl; a phenoxycarbonyl; a benzyloxycarbonyl; a carbamoyl substituted by groups R'_6 and R''_6; a thiocarbamoyl which is free or substituted by one or two C_1-C_7-alkyls; a sulfamoyl; an alkylsulfamoyl or dialkylsulfamoyl in which the alkyl is C_1-C_7; a group $SO_2R'_7$; an alkylsulfonamido in which the alkyl is C_1-C_7; a group COR'_7; a group NR_8R_9 or a group $CO-NH-CH(R_{10})-COR_{12}$; if appropriate, the phenyl group forming part of the substituent R_5 and/or R_6 can be unsubstituted or monosubstituted or polysubstituted by a C_1-C_7-alkyl, a trifluoromethyl, a methoxy, a halogen, a sulfamoyl, an alkylsulfamoyl in which the alkyl is C_1-C_7, a carboxy, an alkoxycarbonyl in which the alkyl is C_1-C_7, a C_1-C_7-acyloxy or an imidazolyl;
- R'_6 and R''_6 are each independently hydrogen, a C_1-C_7-alkyl which is unsubstituted or substituted by R'''_6, a phenyl, a pyridyl, a methylpyridyl, a piperidin-4-yl or a methylpiperidin-4-yl; or R'_6 and R''_6 form, with the nitrogen atom to which they are bonded, a heterocycle selected from piperazine or piperidine;
- R'''_6 is a hydroxy, a cyano, a carboxy which is free or esterified by a C_1-C_7-alkyl or by a benzyl, a phenyl, a pyridyl, a methylpyridyl, an amino which is free or substituted by one or two C_1-C_7-alkyls;
- R_7 is a C_1-C_7-alkyl, a phenyl, a benzyl, a C_3-C_7-cycloalkyl, a C_2-C_4-alkenyl, a C_1-C_7-ω-halogenoalkyl, a C_1-C_7-polyhalogenoalkyl, a C_1-C_7-acyl, a C_1-C_7-ω-carboxyalkyl which is free or esterified by a C_1-C_4-alkyl or by a benzyl, a C_2-C_7-ω-aminoalkyl in which the amino group is free, substituted by one or two C_1-C_4-alkyls or in the form of an ammonium ion;
- R'_7 is a piperazin-1-yl group which is unsubstituted or substituted in the 4-position by a group R''_7, a piperidino group which is unsubstituted or substituted in the 4-position by a group R'''_7, an azetidin-1-yl group which is unsubstituted or substituted in the 3-position by a group R'''_7, a pyridyl group which is unsubstituted or substituted by a methyl;
- R''_7 is a C_1-C_4-alkyl, a phenyl, a benzyl or a C_1-C_4-acyl;
- R'''_7 is R''_7 or an amino which is free or carries a protecting group;

- R_8 and R_9 are each independently a hydrogen, a C_1–C_7–alkyl, a phenyl or a benzyl; R_9 can also be a C_1–C_7–acyl, a C_1–C_7–thioalkyl, a cycloalkylcarbonyl in which the cycloalkyl is C_3–C_7, a cycloalkylthiocarbonyl in which the cycloalkyl is C_3–C_7, a C_1–C_4–ω–aminoacyl, a C_1–C_4–ω–hydroxyacyl, a C_1–C_4–ω–benzyloxyacyl, a phenoxycarbonyl, a thienocarbonyl, a pyridylcarbonyl, a methylpyridylcarbonyl, a C_1–C_4–alkoxycarbonyl, a benzoyl, a group $CO–CH(R_{10})–NR_{11}R'_{11}$, a group $CH(R_{10})CO_2R_{11}$, a group $(CH_2)_tCOR_{12}$, a group $CO(CH_2)_tCOR_{12}$, a carbamoyl which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4 alkyls;
- m is 1 or, if R_6 is a halogen, a C_1–C_7–alkyl or a C_1–C_7–alkoxy, m can also be 2, 3 or 4, or else $(R_6)m$ can be m substituents having different meanings selected from halogen, C_1–C_7–alkyl and C_1–C_7–alkoxy;
- p and q are each an integer, it being possible for their sum to vary from 3 to 6;
- t is an integer which can vary from 1 to 5;
- X is oxygen, sulfur or a group NR_{13};
- R_{10} is hydrogen, a C_1–C_4–alkyl or a benzyl;
- R_{11} and R'_{11} are each independently hydrogen or a C_1–C_4–alkyl;
- R_{12} is a hydroxy, a C_1–C_4–alkoxy or an amino which is unsubstituted or substituted by one or two C_1–C_4–alkyls;
- R_{13} is hydrogen, a C_1–C_4–alkyl, a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1–C_4–alkyls;

and its salts where appropriate.

2. A compound of formula (I) according to claim 1 wherein R_1 is a chlorine atom or an ethoxy group in the 5–position of the indole and R_2 is hydrogen.

3. A compound of formula (I) according to claim 1 wherein R_3 and R_4, together with the carbon to which they are bonded, form a C_3–C_{10} hydrocarbon ring.

4. A compound of formula (I) according to claim 1 wherein R_3 and R_4, together with the carbon to which they are bonded, form a cyclohexane which is unsubstituted or substituted by one or two C_1–C_7–alkyl groups or by a C_3–C_5–spirocycloalkyl, a cycloheptane, an adamantane or a tricyclo[5.2.1.$0^{2.6}$]dec–8–ene.

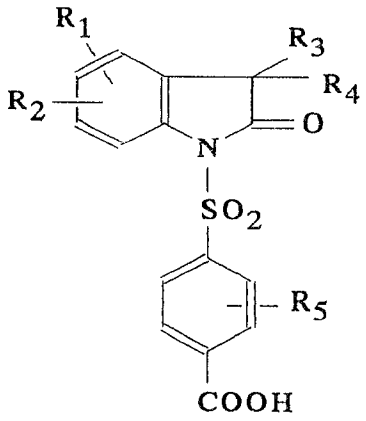
5. compound of formula (I) wherein R_3 and R_4, together with the carbon to which they are bonded, form a piperidine–4 or N–methylpiperidine–4 ring.

6. A compound of formula (I) according to claim 1 wherein R_5 and R_6 are each a methoxy.

7. A compound of formula (I) according to claim 1 wherein R_5 in the 2-position is a methoxy and R_6 in the 4-position is a C_1-C_7-acylamino, a C_1-C_4-dialkylureido or an alkoxycarbonylalkylcarbamoyl in which the alkyl groups are C_1-C_7.

8. A compound of formula (I) according to claim 1 wherein R_1 is in the 5-position and R_2 is hydrogen.

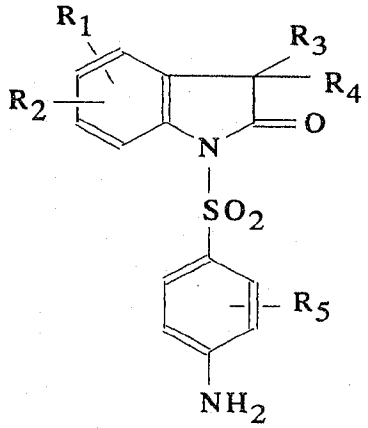
9. A compound according to claim 1 of the formula



(IX)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1, and its functional derivatives.

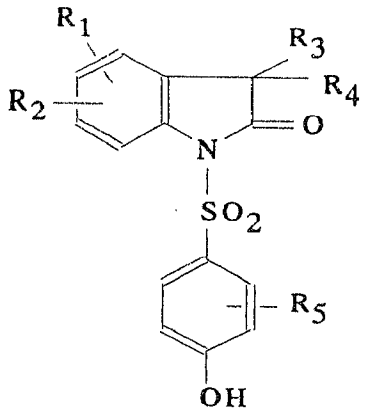
10. A compound according to claim 1 of the formula



(X)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1, and its salts where appropriate.

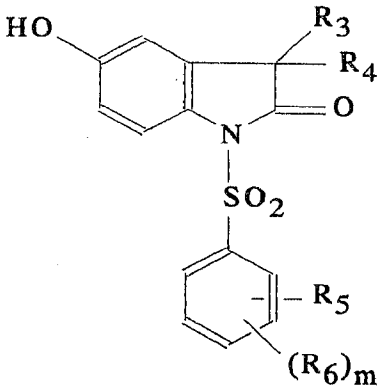
11. A compound according to claim 1 of the formula



(XI)

in which R_1, R_2, R_3, R_4 and R_5 are defined as indicated above for (I) in claim 1.

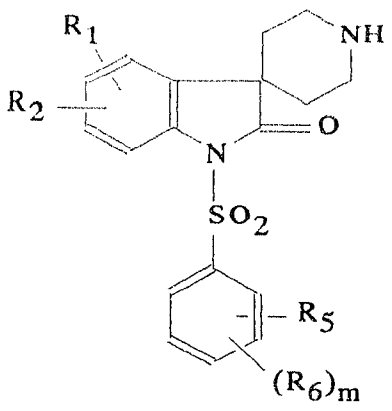
12. A compound according to claim 1 of the formula



(XII)

in which R_3, R_4, R_5, R_6 and m are defined as indicated above for (I) in claim 1.

13. A compound according to claim 1 of the formula

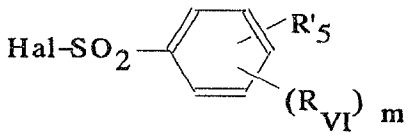


(XIII)

in which R_1, R_2, R_5, R_6 and m are defined as indicated above for (I) in claim 1.

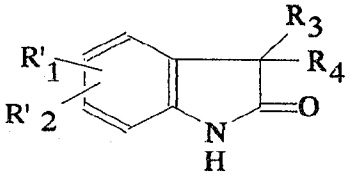
14. A method of preparing a compound (I) according to claim 1, characterized in that:

a benzenesulfonyl halide of the formula



(III)

in which R'_5 and R_{VI} are respectively either R_5 and R_6 as defined above for (I), or precursor groups of R_5 and R_6, is reacted with a 2-oxoindole disubstituted in the 3-position, of the formula



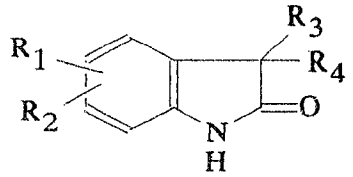
(II)

in which R'_1 and R'_2 are respectively either R_1 and R_2 as defined for (I), or precursor groups of R_1 and R_2, and R_3 and R_4 are as defined above for (I); and

- either, if $R'_1 = R_1$, $R'_2 = R_2$, $R'_5 = R_5$ and $R_{VI} = R_6$, the resulting compound of formula (I) is isolated;
- or, if any one of the groups R'_1, R'_2, R'_5 and R_{VI} is respectively a precursor group of R_1, R_2, R_5 and/or R_6, the compound obtained is subjected to a

subsequent treatment in order to prepare the compound of formula (I) by conversion of any one of the groups R'_1, R'_2, R'_5 and R_{VI} to R_1, R_2, R_5 and R_6 respectively.

15. A compound of the formula



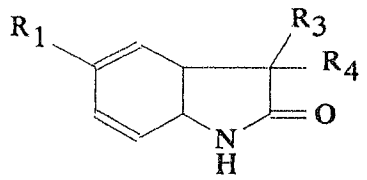
(II)'

in which

- R_1 and R_2 are each independently a hydrogen, a hydroxy, a C_1–C_4–ω–halogenoalkoxy, a halogen, a C_1–C_4–alkyl, a trifluoromethyl, a C_1–C_7–alkoxy, a C_1–C_4–polyhalogenoalkoxy, a C_2–C_4–ω–hydroxyalkoxy, an ω–methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4–ω–aminoalkoxy which is free or substituted by one or two C_1–C_4–alkyls, a C_3–C_7–cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4–alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4–alkyls, a cyano, a C_1–C_4–acyl, a C_1–C_4–acyloxy, a C_1–C_4–alkylsulfonamido, a phenylsulfonamido, a C_1–C_4–alkylamido, a C_1–C_4–alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4–alkyls; and
- R_3 and R_4, together with the carbon to which they are bonded, form
  - an adamantane,
  - an indane or a hexahydroindane which are unsubstituted or substituted by one or more C_1–C_7–alkyl groups,
    a tricyclo[5.2.1.$0^{2.6}$]decane or a tricyclo[5.2.1.$0^{2.6}$]dec–8–ene which are unsubstituted or substituted by one or more C_1–C_7–alkyl groups,
    or
    a C_4–C_8 hydrocarbon ring substituted by one or more C_1–C_7–alkyl groups or by a C_3–C_5–spirocycloalkyl; or else
- R_3 and R_4 together form a group $-(CH_2)_p-X(CH_2)_q-$ in which p and q are integers whose sum can vary from 3 to 6 and X is oxygen, sulfur or a group NR_{13}, R_{13} being a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1–C_4–alkyls,

with the limitation that if CR_3R_4 is adamantane, R_1 and R_2 are other than hydrogen.

16. A compound of the formula



(II)"

in which

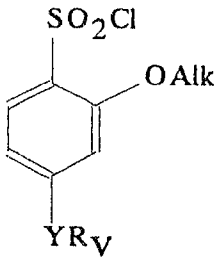
- R_1 is a hydroxy, a C_1–C_4–ω–halogenoalkoxy, a halogen, a C_1–C_4–alkyl, a trifluoromethyl, a C_1–C_7–alkoxy, a C_1–C_4–polyhalogenoalkoxy, a C_2–C_4–ω–hydroxyalkoxy, an ω–methoxyalkoxy in which the alkyl is C_2–C_4, a C_2–C_4–ω–aminoalkoxy which is free or substituted by one or two C_1–C_4–alkyls, a C_3–C_7–cycloalkoxy, a cycloalkylmethoxy in which the cycloalkyl is C_3–C_7, a phenoxy, a benzyloxy, a C_1–C_4–alkylthio, a phenylthio, a nitro, an amino which is free or substituted by one or two C_1–C_4–alkyls, a cyano, a C_1–C_4–acyl, a C_1–C_4–acyloxy, a C_1–C_4–alkylsulfonamido, a phenylsulfonamido, a C_1–C_4–alkylamido, a C_1–C_4–alkoxycarbonylamino or a ureido which is unsubstituted or substituted by a phenyl or by one or two C_1–C_4–alkyls;
- R_3 and R_4 together form a group $-(CH_2)_pX(CH_2)_q-$;
  or
- R_3 and R_4, together with the carbon to which they are bonded, form an optionally fused, saturated or unsaturated C_3–C_{10} hydrocarbon ring which is unsubstituted or substituted by one or more C_1–C_7–alkyl groups or by a C_3–C_5–spirocycloalkyl;
- p and q are each an integer, it being possible for their sum to vary from 3 to 6;
- X is oxygen, sulfur or a group NR_{13}; and
- R_{13} is hydrogen, a C_1–C_4–alkyl, a phenyl, a benzyl, a C_1–C_4–acyl, a C_1–C_4–alkoxycarbonyl or a carbamoyl which is unsubstituted or substituted by one or two C_1–C_4–alkyls,

with the limitation that

- if R_1 is methoxy, CR_3R_4 is other than a pyrrolidine–3 which is unsubstituted or N–substituted by a C_1–C_4–alkyl, and if R_1 is a halogen, CR_3R_4 is other than a pentane.

17. A compound according to claim 16 in which R_1 is ethoxy.

18. A compound of the formula



(III)'

in which

- Alk is a C_1–C_7–alkyl;
- Y is O or S; and
- R_V is a C_1–C_7–alkyl, a C_3–C_7–cycloalkyl, a C_2–C_4–alkenyl, a C_1–C_7–ω–halogenoalkyl, a C_1–C_7–polyhalogenoalkyl, a benzyl, a C_1–C_7–acyl or a C_1–C_7–ω–carboxyalkyl esterified by a C_1–C_4–alkyl or by a benzyl.

19. Pharmaceutical composition in which a compound according to any one of claims 1 to 8 is present as the active principle.

20. Pharmaceutical composition in which a compound according to any one of claims 1 to 8 is present in association with another active principle.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente